WHO Drug Information

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CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
Health Canada Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA Health Products Regulatory Authority, Ireland (www.hpra.ie)
HSA Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA International Conference of Drug Regulatory Authorities
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP International Generic Drug Regulators Programme (https://www.igdrp.com)
MHLW Ministry of Health, Labour and Welfare, Japan
MHRA Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int The International Pharmacopoëia (http://apps.who.int/phint/)
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
PMDA Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S. United States of America
WHO World Health Organization (www.who.int)
WHO EMP WHO Essential medicines and health products (www.who.int/medicines/en/)
WHO PQT WHO Prequalification team (https://extranet.who.int/prequal/)

Note: The online version of this issue (freely available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and websites referenced.
INTERNATIONAL ATOMIC AGENCY (IAEA)/WHO
GUIDELINES ON GOOD MANUFACTURING PRACTICES
FOR RADIOPHARMACEUTICAL PRODUCTS
(July 2019)

DRAFT FOR COMMENTS

Medicines Quality Assurance working documents will be sent out electronically only. They will also be placed on the Medicines website for comment under “Current projects”. http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

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INTERNATIONAL ATOMIC AGENCY (IAEA)/WHO
GUIDELINES ON GOOD MANUFACTURING PRACTICES
FOR RADIOPHARMACEUTICAL PRODUCTS

1. SCOPE OF THESE GUIDELINES

These guidelines are intended to provide a general overview of the minimum Good Manufacturing Practices (GMP) requirements for radiopharmaceuticals. The main principles of GMP are described in detail in the chapters for pharmaceutical products (1,2) as well as those for sterile pharmaceutical products (3). Unless otherwise specified, the GMP requirements for radiopharmaceuticals described in this guidance should take precedence over the GMP requirements for pharmaceutical products.

The procedures necessary to manufacture and control radiopharmaceutical products are in large part determined by the nature of these products, the methods of manufacture and their intended use. The recommendations in these guidelines are applicable to the following scenarios:

- The production or compounding of radiopharmaceuticals in hospital radiopharmacies, including diagnostic and therapeutic products.
- The production or compounding of radiopharmaceuticals in centralized radiopharmacies.
- The production or compounding of radiopharmaceuticals in nuclear centres and institutes.
- The production of radiopharmaceuticals by industrial manufacturers.
- The production of cyclotron-based positron emission tomography (PET) radiopharmaceuticals.

The scope of this guidance does not include the following:

- Radiopharmaceutical dispensing (i.e. the drawing of a patient specific unit dose from a bulk vial of a radiopharmaceutical).
- Regulatory authority-approved radiopharmaceutical preparation (i.e. the use of approved kits and approved generators in order to produce a radiopharmaceutical product as per instructions of the marketing authorization holder).
- Handling of ready-to-administer radiopharmaceutical products (e.g. receipt, storage, assay, etc.).
- Production or compounding of non-radioactive compounds, including cold kits.
- Production of investigational radiopharmaceuticals.
2. DEFINITION OF TERMS

“As Low As Reasonably Achievable” (ALARA)
A set of practices designed to ensure the minimum necessary worker radiation exposure. These practices are based on the principles of time, distance, shielding and awareness.

Dispensing
The generation of a patient-specific unit dose which involves the physical withdrawal of the radiopharmaceutical from the bulk single-use or multi-dose vial into a syringe, dilution with appropriate diluent as necessary, measurement and labelling the syringe.

Good Manufacturing Practices for radiopharmaceuticals
A set of practices, using a traceable process, which ensures that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use and designed to consistently yield the radiopharmaceutical product. Good Manufacturing Practices fall under the umbrella of the overall Quality Management System.

Manufacturing or production
Within the scope of this guidance, these terms refer to all the operations performed leading up to the finished radiopharmaceutical product, including the purchase of starting materials, production, quality control (QC), release and storage of radiopharmaceuticals.

Preparation or kit-reconstitution
Within the scope of this guidance, preparation or kit reconstitution refers to all the procedures carried out as per instructions from marketing authorization holder which involves addition of radionuclide solution approved by regulatory authorities to an approved cold kit.

Primary packaging
Any packaging material that comes into direct contact with the radiopharmaceutical finished product (i.e. an immediate container, such as a vial or a syringe).

Quality control
A set of analytical tests designed to demonstrate compliance of the quality of starting materials, intermediates and radiopharmaceutical final products with pre-determined quality acceptance specifications.

Quality Management System
An appropriate system encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will satisfy the given requirements for quality.
Radiopharmaceutical compounding
This term refers to producing radiopharmaceuticals with no marketing authorization but pursuant to a physician’s order for a specific patient or patients. In various regions of the world, this practice may also be referred to as “in-house preparation”, “in-house-manufacturing” or “hospital preparation.”

Radiopharmaceutical product
Any pharmaceutical product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medicinal purposes.

Secondary packaging
The shielded container housing the primary packaging.

3. QUALITY MANAGEMENT SYSTEM

3.1 One of the main goals of any manufacturing process is to consistently yield a product of intended quality. The Quality Management System (QMS) is an appropriate system, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will satisfy the given requirements for quality.

3.2 QMS is part of the manufacturer’s overall commitment to establish manufacturing process controls that comply with applicable regulations and consistently yield a product of acceptable quality. These manufacturing process controls are also known as Good Manufacturing Practices (GMP).

3.3 While the terms QMS and GMP also apply to the manufacture of “traditional” pharmaceuticals, the actual requirements of controls for radiopharmaceutical manufacturing are quite different from the requirements for “traditional” pharmaceutical manufacturing and should be based on a well-defined and appropriate risk assessment.

3.4 Risk assessment and risk management are the key concepts applied when establishing manufacturing process controls intended to minimize the risk of unnecessary patient harm, resultant from the suboptimal quality of the product. Risk assessment involves a thorough evaluation and identification of all possible risks associated with the manufacturing process and risk management involves implementing measures to minimize those risks.
3.5 Risk management measures should be based on consideration of the complexity of the intended process. Because radiopharmaceuticals are significantly different from “traditional” medicines, both in their characteristics and the production process, the GMP requirements applicable to the manufacture of “traditional” pharmaceuticals cannot be applied in their entirety to the manufacture of all classes of radiopharmaceuticals.

3.6 Radiopharmaceutical specific characteristics generally include the following:

- simple distribution chain, with direct delivery of the finished product from the manufacturer to the nuclear medicine department;
- small batch size;
- limited shelf-life of minutes to several days;
- quality control (QC) sample representing the entire batch;
- diagnostic radiopharmaceuticals often possess low potential to exert pharmacological or toxic effects due to the micro-dose levels administered.
- Radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility, endotoxin content determination and radionuclidic purity, may need to be performed post-release. Hence, the importance of the application of GMP is essential to minimize the possible risks to the quality that may not be identified through QC pre-release testing. Qualification of instruments/equipment and validation of methods/processes are essential to prove that the critical aspects of their operation are controlled.

3.7 The unique nature of these agents requires specialized risk management that is tailored to the actual production process, the nature of the radiopharmaceutical itself, the level of risk associated and the clinical indication. As always, the radioactive nature of these agents requires compliance with “as low as reasonably achievable (ALARA) principles” (4,5). The recommendations provided in this guidance are based on such reasoning.
4. QUALIFICATION AND VALIDATION

4.1 Qualification of instruments/equipment and validation of methods/procedures are essential to prove that the critical aspects of their operation are controlled.

4.2 Validation and qualification activities should be planned in an orderly manner and documented.

4.3 Qualification of premises, supporting utilities, production and QC equipment should demonstrate that they have been designed (if applicable), installed, operated and perform in accordance with the requirements of GMP and are fit-for-purpose.

4.4 The planning of qualification and validation activities should consider the complexity and critical aspects of the intended radiopharmaceutical production. A schedule of planned preventive maintenance should be established for instruments/equipment as well as regular verifications and/or calibrations as appropriate. These commitments must be documented in a written and approved standard operating procedure (SOP).

4.5 Process validation should be carried out after all other qualification and validation have been successfully completed.

4.6 Process validation should include an adequate number of productions of the intended radiopharmaceutical(s), prepared following the same procedures, covering the intended batch size range and with the same production, quality specifications and acceptance criteria as of typical intended routine batches. The number of batches and the batch size range should be pre-determined as part of a risk assessment performed prior to process validation.

4.7 Cleaning validation should be especially focused on critical production areas, such as working surfaces, and in general surfaces which come into direct contact with the operators or with starting materials, intermediates and finished products.

4.8 Analytical methods should be validated in case they are not described in any recognized source (e.g. a pharmacopoeia). Compendial analytical methods, already described in a recognized source, are not required to be validated; however, method suitability under actual conditions of use should be performed and documented.

4.9 General principles on validation of analytical methods may be found following suitable guidelines (6,7); however, the unique nature of radioactivity should be considered, and specific adaptations should be made, if justified.
4.10 **Re-validation of critical processes (e.g. media fill studies) should be performed on a periodic basis.** These commitments must be documented in a written and approved SOP. Re-validation of any process or requalification of equipment may be warranted under certain circumstances (e.g. in case of significant changes and/or of deviations which may affect the quality of the product).

4.11 Validation/qualification activities, including clearly defined responsibilities and the resultant data, should be documented and archived.

4.12 Processes and procedures should ultimately be established based on the results of the validation performed.

5. **PRODUCT COMPLAINTS**

5.1 There should be a written SOP for handling and investigating product complaints.

5.2 The SOP should also describe the actions to be taken in case of complaints.

6. **PRODUCT RECALL**

6.1 There should be a SOP for product recall.

6.2 Since the return of radioactive products is generally not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with international and national transport regulations (8).

7. **CONTRACT PRODUCTION, ANALYSIS AND OTHER ACTIVITIES**

7.1 Sub-contractors should be qualified as per internal written approved procedure. The respective responsibilities of each party must be clearly defined.
8. PERSONNEL AND TRAINING

8.1 The manufacturing establishment should have adequate personnel to carry out the intended operations. The responsibility placed on any one of the personnel should not be so extensive as to present an increased risk to the quality. The manufacturing establishment and its personnel should be under the supervision of a responsible person(s) who possesses qualifications and practical experience or as required by national legislation.

8.2 Supporting personnel should have the necessary training and experience appropriate to their function.

8.3 Personnel should be trained on SOPs related to radiopharmaceutical manufacture, approved by the responsible person.

8.4 To ensure the safe manufacture of radiopharmaceuticals, personnel should also be trained in GMP, the safe handling of radioactive materials and radiation safety procedures. Personnel should take periodic courses and receive training to keep abreast of the latest developments in their fields.

8.5 Training should be planned and documented, and the training records should be retained in a personnel file.

8.6 All personnel handling radioactivity should be monitored for possible contamination and/or irradiation exposure.

8.7 Personnel working in clean areas should maintain good personal hygiene. Personnel are required to report to the immediate supervisor any condition that may potentially adversely affect the product.

9. PREMISES

9.1 As a general principle, facilities must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials should be designed to take into consideration aspects of radiation protection and ALARA compliance, in addition to cleanliness and controls to minimize microbial contamination.
9.2 Lighting, heating, ventilation and air-conditioning systems should be designed to maintain an appropriate temperature and relative humidity in order to ensure the proper equipment function, material storage conditions and safety and comfort of personnel.

9.3 Facilities should be maintained in a good state of operation. Special precautions should be exercised to ensure that facility repair or maintenance operations do not compromise product quality. Premises should provide adequate space for the operations to be carried out, allowing an efficient workflow and effective communication and supervision. Facilities should be designed to have controls to prevent the risk of entry of insects, pests and vermin.

9.4 **Interior** surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks; they should not shed matter and should permit easy cleaning and decontamination.

9.5 Drains should be avoided wherever possible and, unless essential, should be excluded from clean areas.

9.6 Sinks should be excluded from clean areas.

9.7 Pipework, valves and vent filters should be properly designed to facilitate cleaning and decontamination.

9.8 Technical area (e.g. rooms to access the rear of hot cells) access points should be configured in a way to minimize the entrance of the maintenance/technical personnel to the production/clean areas.

9.9 The pressure regime and ventilation system for the different facility areas should be carefully established to both minimize the risk of product contamination and to protect the personnel from unnecessary radiation exposure. The pressure differentials should be monitored.

9.10 Radioactive gas emissions should be effectively monitored, including alarms, in order to minimize the risk of unnecessary radiation exposure to personnel as well as to the surrounding environment.

9.11 Radioactive gas exhausts should be removed via a separate air handling unit through appropriate filters that are regularly checked for performance.
9.12 All operations of radioactivity handling, storage and waste disposal should be performed in compliance with national regulations and guidance.

9.13 A dedicated area and equipment should be used for the manufacture of any radiopharmaceutical product involving human blood or plasma.

9.14 A manufacturer’s QC laboratory should be in a separate dedicated area.

10. **EQUIPMENT**

10.1 Equipment used should be qualified for the intended purpose through appropriate design, specifications, installation, calibration, operation, and maintenance. Critical factors, including minimizing the risk of product contamination, minimizing the risk of staff radiation exposure and optimised ergonomics, should be considered during equipment design (design qualification) in order to facilitate their operation, maintenance and cleaning. Subsequently, before use, equipment should be qualified for the intended purpose by performing installation qualification, operational qualification and performance qualification, records of which are to be retained (9).

10.2 Equipment used for radiopharmaceutical manufacture and QC should be periodically calibrated and maintained.

10.3 Equipment maintenance, qualification, and calibration operations should be recorded and archived in proper log-books.

10.4 Equipment controlling software may be considered as part of the equipment and, therefore, may be included in the process of equipment qualification.

10.5 SOP’s should be established for the operation, calibration, and planned preventative maintenance (PPM) of the equipment.

10.6 The dose calibrator (also known as activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.
11. **STARTING MATERIALS**

11.1 Starting materials of appropriate quality should be used for radiopharmaceutical production. Written material acceptance SOPs must be established for starting materials to be subsequently used in radiopharmaceutical production.

11.2 Specifications for every starting material must be established. Examples of such specifications may include identity, purity or certification of origin (if applicable) and any other parameter or characteristic that makes the material suitable for the intended use.

11.3 Starting materials could be accepted by either performing in-house testing or a review of the Certificate of Analysis (CoA) supplied by the reliable material manufacturer to confirm compliance with the internal acceptance specification.

11.4 Materials should be segregated into three separate categories: (1) accepted materials, (2) quarantined material, and (3) rejected materials and labelled accordingly.

11.5 Rejected materials must be securely stored in an area separate from the rest of the materials.

11.6 Waste materials should be disposed of in accordance with the national requirements.

12. **DOCUMENTATION**

12.1 Good documentation practices should be used.

12.2 Documents should ensure the traceability of radiopharmaceutical production (including the processes and the product).

12.3 The processing records of regular production batches must provide a clear and complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and delivered in accordance with the applicable SOPs.
12.4 A controlled system of written SOPs must be created to cover the requirements for major aspects of radiopharmaceutical manufacturing. The SOPs should be approved, signed and dated by the appropriate responsible person(s). No approved SOP document should be changed without an appropriate review, evaluation and approval by the responsible person(s). The SOPs should be reviewed periodically to ensure applicability.

12.5 Documentation should be retained for a period appropriate to the nature of the document content.

13. **GOOD PRACTICES IN PRODUCTION**

13.1 Access to restricted areas should be by authorized and trained personnel only.

13.2 Only the minimum number of personnel required should be present in clean areas.

13.3 Processes should be designed to minimize the risk of contamination, cross-contaminations and mix-ups. The following measures may be adopted to minimize these risks:

   (a) processing and filling in segregated areas;
   (b) avoiding the manufacture of different products at the same time, in the same dedicated space or by the same personnel;
   (c) performing manufacturing area decontamination and visual pre-checks;
   (d) using manufacturing “closed systems”, whenever possible.

13.4 The critical aseptic operations, such as final product vial assembly, vial filling or sterility testing, should be carried out in areas under high efficiency particulate air (HEPA) filtered laminar air flow (10).

13.5 Both raw materials and final radiopharmaceutical products should be stored under appropriate controlled conditions.

13.6 An evaluation program aimed to define the stability of the finished products should be established.

13.7 The expiration dates and times for radiopharmaceuticals should be based on the results of an adequate number of stability studies.
14. **GOOD PRACTICES IN QUALITY CONTROL**

14.1 Radiopharmaceuticals final product acceptance criteria, including criteria for release, should be established and documented in a written SOP.

14.2 Sampling procedures should consider the nature and the characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content) to make sure that the samples are representative of the batch of radiopharmaceutical.

14.3 The QC procedures should be described in written SOPs.

14.4 QC samples should be prepared, handled and stored in a way to ensure the adequate identification and segregation of the test samples to avoid mix-ups and cross-contamination.

14.5 Radiopharmaceutical final products failing to meet the acceptance criteria should be rejected and segregated. Such events should be investigated; and the investigation outcome and proposed actions should be documented.

14.6 The release of a batch should be performed by a responsible person.

14.7 In the manufacturer setting, batch release should be carried out by the responsible person or Persons separate from the person or persons carrying out production and QC.

15. **LABELLING**

15.1 Radiopharmaceutical final products should be clearly identified by labels.

15.2 Whenever possible, a portion of the primary packaging container should be left uncovered to allow for the inspection of contents.

15.3 The content of the labels for radiopharmaceutical products must comply with the relevant national regulations and international agreements.
In the absence of regulatory authority requirements, the following information may be listed on the primary packaging container label:

(a) the name of the product and batch number;
(b) the name of the manufacturer;
(c) the amount of activity in SI units;
(d) for liquid radiopharmaceuticals, the total activity or the radioactive concentration per millilitre at calibration date and, if necessary, time, and the volume of liquid;
(e) for capsules, the radioactivity of each capsule at calibration date and, if necessary, time, and the number of capsules in the container;
(f) where relevant, the international symbol for radioactivity;
(g) expiration date and time;
(h) cautionary statements, e.g. “Caution: radioactive material”.

Please note that reporting information about activity on a primary label may not always be possible due to radiation protection reasons; in this case, they may be reported on the secondary packaging label only.

In the absence of regulatory authority requirements, the following information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:

(a) the qualitative and quantitative composition;
(b) excipient information;
(c) the route of administration;
(d) any special storage instructions; and
(e) the address of the manufacturer.

**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALARA</td>
<td>“As Low As Reasonably Achievable”</td>
</tr>
<tr>
<td>CoA</td>
<td>Certificate of Analysis</td>
</tr>
<tr>
<td>GMP</td>
<td>good manufacturing practices</td>
</tr>
<tr>
<td>HEPA</td>
<td>high efficiency particulate air</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>PPM</td>
<td>planned preventative maintenance</td>
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<tr>
<td>QC</td>
<td>quality control</td>
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<td>QMS</td>
<td>quality management system</td>
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<td>SOP</td>
<td>standard operating procedure</td>
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7. ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: Text and Methodology, Step 4 of the ICH Process, November 2005


10. EN ISO 14644.

Additional Reading


https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1662web-89688003.pdf


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WHO GUIDELINE ON THE IMPLEMENTATION
OF QUALITY MANAGEMENT SYSTEMS
FOR NATIONAL REGULATORY AUTHORITIES

(July 2019)

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http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.

Note from WHO Secretariat: this working document was prepared by the Regulatory Systems Strengthening (RSS) Group with the support of the Medicines Quality Assurance (MQA) Group.
WHO GUIDELINE ON THE IMPLEMENTATION
OF QUALITY MANAGEMENT SYSTEMS
FOR NATIONAL REGULATORY AUTHORITIES

1 BACKGROUND

Implementation of the Thirteenth World Health Organization (WHO) General Programme of Work (2019-2023), as adopted by the Seventy-First World Health Assembly (2018) and the WHO Leadership Priorities, has attracted much international public health attention to the theme of Universal Health Coverage and to increased access to safe and effective medical products.

Several World Health Assembly (WHA) resolutions, including WHA67.20 (2014), mandate WHO to provide support to its Member States (MS) in strengthening national regulatory systems for medical products. It recognizes that “effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes; that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products” [1]. Accordingly, to facilitate access to these products, WHO’s vision is for all MS to have a regulatory system that ensures medical products and other health technologies in the market meet internationally recognized standards of quality, safety and efficacy.

National Regulatory Authorities (NRAs) are responsible for ensuring safety, quality and efficacy of medical products within the respective MS, demonstrating that the services they provide consistently meet legal and regulatory requirements, delivering effective and efficient services, evaluating performance and making improvements. A quality management system (QMS) can ensure that the products or services an NRA provides consistently meet statutory and regulatory standards and meet customers’ expectations. A QMS provides opportunities to enhance customer satisfaction, address context-associated risks and opportunities for continuing improvement, demonstrate conformity to specific QMS requirements, and assure the quality, safety and efficacy of medical products.
In 2015, WHO developed and launched the WHO Global Benchmarking Tool (GBT). This tool assists regulators worldwide in evaluating the developmental status of their regulatory system and its related functions. The GBT includes one indicator that assesses the NRA’s level of development with respect to QMS.¹ Benchmarking results of low and middle-income countries indicate that most NRAs need to establish and implement a QMS or, if already established, enhance and maintain the QMS.

QMS implementation is challenging for NRAs due to the diversity of NRA legal mandates and organizational structures, to the different levels of NRA development and to the number of regulatory functions that need to be addressed. WHO has developed this guideline to respond to requests by MS to have an international guideline on implementation of QMS by NRAs.

2 OBJECTIVE

The aim of this guideline is to assist NRAs to develop, implement and improve QMSs based on principles from International Standardisation Organization (ISO) document ISO 9001 Standard requirements [2]. It provides recommendations on what NRAs should implement and maintain under the QMS to effectively and efficiently support the execution of NRA functions as mandated by national laws and regulations. The guideline is expected to promote consistency in regulatory practices within and across NRAs to facilitate harmonisation, mutual reliance and recognition mechanisms among MS.

Therefore, the guideline has the following objectives:

a) Describe principles for implementing a QMS to support planning, execution, monitoring and evaluation of performance of all applicable functions and activities for NRAs.

b) Provide requirements for the QMS to support and facilitate systematic linkages and integration of different processes and systems of the regulatory functions and activities within NRAs.

c) Provide requirements that NRAs should consider for evaluating the performance of the QMS and measures that the NRA should implement for continually improving the QMS.

¹ References to the GBT VI.
3 SCOPE OF THE GUIDELINE

This is an overarching guideline that should be applied across all regulatory functions and activities, including registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspections, laboratory access and testing, clinical trials oversight, national lot release and others as applicable to the implementing NRA. The guideline should be implemented to cover all types and categories of medical products and technologies under the responsibility of an implementing NRA.

The guideline can be used for other regulatory activities which are mandated by the national laws and regulations to ensure public health safety by assuring quality, safety and effectiveness of medical products. This extends to areas of medical products pricing, professional training and regulation and procurement of medical products, as well as to other areas within the legislative mandates and functions of the NRA.

This guideline provides recommendations for QMS implementation for all models of NRAs. NRAs can be legally, organisationally and operationally structured as follows:

a) **Discrete** – two or more institutions involved in partial or full enforcement of national laws and regulations for medical products in a country (e.g. one institution with legal mandates to enforce marketing authorizations (MAs) and another one within the same country for licensing establishments (LI) regulatory function).

b) **Decentralised** – one NRA with full legal mandates to enforce national laws and regulation of medical products within the country. Legally defined amount of enforcement, authority and operations are executed in localised zones or geopolitical zones of the country while the rest is enforced at country level. This model exists in MS having a federal governance system where laws and regulations are enforced at state/province and national levels.

c) **Centralised** – one NRA with full legal mandates to enforce national laws and regulation of medical products within the country. The enforcement, authority and operations are executed, managed and controlled centrally for all applicable regulatory functions and activities.
The provided recommendations are applicable to all sizes as the principles and intended results remain the same regardless of the complexity of NRA. Therefore, this guideline describes the requirements which should be implemented; the MS and respective NRAs reserve the right to decide on how to address these requirements within the existing contexts and provisions of the laws. This guideline can be utilized by institutions which are responsible for single or multiple specific regulatory functions related to medical products.

Use of this guideline is voluntary. NRAs are free to use this guideline or to choose other methods for implementing QMS. The implemented QMS should be demonstrated by documented evidence to have systematic processes which are controlled, maintained and evaluated for continuous improvement. NRAs are free to use any appropriate national or international standard or guideline as a basis for the implementation of the QMS.

Where different units within the NRA have already implemented QMS for specific regulatory functions (such as laboratory testing and/or regulatory inspection), this guideline could be used by the NRA to determine the functions and processes that have not been addressed by the already implemented management systems. This is to avoid duplications and overlaps of management systems and to ensure gradual integration of all existing management systems with the overall QMS of the NRA. The implementing NRA should determine the extent to which this guideline should be implemented without leaving out any of its processes and activities that are mandated by national laws and regulations.

Effective implementation of this guideline will not lead to any WHO certifications and WHO will not conduct any audits for verification of implementation of QMS for already certified NRAs. However, as part of the regulatory systems strengthening program, WHO will conduct the benchmarking of the MS regulatory functions including QMS related processes using the GBT to determine the strengths and gaps, if any, for capacity building and continuous improvements. This guideline should be implemented to cover regulatory functions which are part of the GBT and other functions and activities of the NRA that are addressed by national laws and regulations but which are not part of the GBT. References to GBT VI [6] provides a linkage of GBT indicators with the relevant chapters of this guideline.

The guideline should be implemented on the foundation of the principles and recommendations as provided in the current version of WHO guideline on Good Regulatory Practices (GRP) [3]. The implementation of the QMS should ensure that the GRPs are integrated to the extent possible without affecting the effectiveness and efficiency of the NRA to execute its functions.
4 GLOSSARY

The definitions given below apply to the terms used in this guideline which are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

**Competence**
Knowledge, skills and attitude required for successful work performance.

**Correction**
Any action that is taken to eliminate a nonconformity. However, corrections do not address causes.

**Corrective actions**
Steps that are taken to eliminate the causes of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again.

**Customer**
A person or organization that could or does receive a product or a service that is intended for or required by this person or organization. Customers of NRA include individuals or parties who receive or could receive and use products and services which are provided and offered by NRA. These parties include the general public, patients, manufacturers, distributors, health practitioners, researchers, Ministry of Health (MOH) and other individuals and intuitions that rely on the NRA products and services to make public health decisions.

**Customer satisfaction**
A customer's perception of the degree to which the customer's expectations have been fulfilled. This relates to the expectations that different parties have from the NRA. The expectations include assurance that safe, efficacious and high-quality medical products will be available under the NRA mandate to regulate and that the NRA will provide other products such as guidelines, public reports and related regulatory services that meet the expectations of different types of customers.

**Internal audit**
An examination and assessment of all or part of a quality system with the specific purpose of improving it. An internal audit is usually conducted by an independent (i.e., of the function to be audited) and qualified team of experts designated by the management for this purpose.
Process
A set of interrelated or interacting activities that use inputs to deliver an intended result.

Product
Output of an organization that can be produced without any transaction taking place between the organization and the customer. They are also called regulatory products in this guideline. Products of NRAs relate to the tangible items which the NRA produces for its customers. These items include regulatory guidelines, public health notices, guidance notes, alerts, databases, mobile phone applications, reports and other materials which are intended to provide regulatory information and communications to customers. Before their production, some of these products may require lengthy consultations for designing them.

Quality
The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs and to ensure the consistent and reliable performance of services or products in conformity with specified requirements.

Quality Management System (QMS)
An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

Quality policy
A brief statement that describes the organization’s purpose, overall intentions and strategic direction, provides a framework for quality objectives and includes a commitment to meet applicable requirements.

Senior (Top) management
Person(s) who direct and control a company or site at the highest levels and who have the authority and responsibility to mobilize resources within the company or site. In NRAs, senior management or top management (TM) can be used interchangeably.

Services
Output of an organization with at least one activity necessarily performed between the organization and the customer. They are also called regulatory services in this guideline. This includes, for example, activities such as evaluation of applications for market authorisations, inspections of facilities and testing of health product samples.
NRAs should implement a QMS that is supported by the process approach concept, Plan-Do-Check-Act (PDCA) cycle and risk-based thinking. NRAs should ensure that the implemented QMS meets its needs without making it unnecessarily complex to avoid it negatively affecting its effectiveness and efficiency. The QMS should be simple, fit-for-purpose and understandable.

An effective QMS should be implemented based on internal processes as identified and documented by the NRA from the input requirements, through the intermediate activities, and up to the output results shown in Figure 1.

![Figure 1: Process approach (ISO 9001:2015[2])](image)

The PDCA cycle requires NRAs to carry out planning, performing (implementing), checking (evaluating) and acting (to improve) processes in the QMS. The applied PDCA cycle covering the chapters in this guideline is provided in Figure 2. ISO 9001 standard [2] provides the following brief description of the PDCA process:

- **Plan**: establish the objectives of the system and its processes, obtain the resources needed to deliver results in accordance with customers’ requirements and the NRA’s policies, and identify and address risks and opportunities.
- **Do**: implement what was planned.
- **Check**: monitor and, where applicable, measure processes and the resulting products and services against policies, objectives, requirements and planned activities and report the results.
- **Act**: take actions to improve performance, as necessary.
The context of NRA and scope of its QMS are placed in the middle to provide the limitations to which the QMS should be implemented.

Leadership and management are centrally indicated as they are important requirements for effective QMS implementation. TM should commit and support all QMS processes from planning up to acting for continuous improvement.

Document and data management are centrally indicated because they should be part of every step of the PDCA cycle in the form of procedures, forms and records that facilitate the consistent implementation of QMS processes and record retention.

Risk-based thinking (included in planning stages) enables NRAs to identify factors that could cause QMS processes to deviate or that could prevent the planned results from being achieved, to put in place proactive measures and controls to minimize the impact of negative effects, and to leverage opportunities as they arise. Risk based thinking is applicable and should be implemented throughout the PDCA cycle.

Figure 2: Applied PDCA cycle
NRAs should implement a QMS that identifies and integrates other management system standards that are applicable to the processes. The management systems which are for specific areas and processes should be documented. The NRA should ensure that the management systems do not create duplications, overlaps or inconsistencies within the overall QMS. While other WHO guidelines have been implemented for management systems of specific regulatory functions such as inspections and quality control testing, the overall QMS should be consistently implemented throughout the organisation across different regulatory functions and other supporting areas.

QMSs are influenced by the different policies, objectives, diverse work methods, resource availability and administrative practices specific to each NRA. NRAs are free to decide the mode and routes to use when implementing this guideline as long as the implemented QMS yields effective, consistent and reliable results in the regulation of medical products.

Effective implementation of this guideline by NRAs should be supported by the following principles as provided in ISO 9000 [4]:

**Customer focus.** The primary focus of a QMS is to meet customer requirements and to strive to exceed customer expectations. In this guideline, customer focus means meeting the needs and expectations of the public, patients, healthcare practitioners, manufacturers, researchers and procurers by providing regulatory products and services which assure access to high-quality, safe, effective and affordable medical products and health technologies.

**Leadership.** Leaders at all levels establish unity of purpose and direction and create conditions in which people are engaged in achieving the NRA’s planned objectives.

**Engagement (involvement) of people.** Competent, motivated, empowered and engaged people at all levels throughout the organization are essential to enhance the organization’s capability to create and deliver value.

**Process approach.** Consistent and predictable results are achieved more effectively and efficiently when activities are understood and managed as interrelated processes that function as a coherent system. This is critical as it avoids having systems which are based on individuals within NRA.

**Improvement.** Successful organizations have an ongoing focus on improvement. The NRA should ensure that it strives continuously to improve its processes within the QMS.
Evidence-based decision-making. Decisions based on the analysis and evaluation of data and information are more likely to produce desired results. This requires NRAs to implement measures for monitoring, analysing and evaluating the collected data to assess if the processes are delivering the desired results.

Relationship management. For sustained success; organizations manage their relationships with relevant interested parties. Implementing an effective QMS requires the NRA to ensure that its relationships are managed strategically for continuous operations. The relationships include management of contractual agreements for activities subcontracted to individuals and institutions. The areas with subcontract agreements would either be technical or administrative and, if not managed properly, may have negative effects on the effective implementation of the QMS.

The QMS requirements which are described in the subsequent sub-chapters have descriptions of what NRAs should implement as part of their overall QMS. Table 1 provides a summary and focus for each sub-chapter.

Table 1. Summary of QMS requirements for each sub-chapter

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<th>Summary of requirements for implementation in QMS</th>
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<td>The requirements of this chapter focus on NRA describing and documenting the setup of its QMS. The setup includes:</td>
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<td>• Legislative mandates (functions) of the NRA,</td>
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<td>finances and accounting, environment, occupational health and safety, workflow,</td>
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<td>customer relationship management, MOH policies and strategic action plans.</td>
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<tr>
<td>Scope of the</td>
<td>This chapter describes requirements for NRAs to document the processes that are covered by the implemented QMS.</td>
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<tr>
<td>QMS</td>
<td>All processes and activities that are done by the NRA as mandated by national laws and regulations should be included in the QMS.</td>
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<td><strong>Context for NRAs</strong></td>
<td>The focus is to provide guidance regarding what should be indicated when describing and documenting the setup of the NRA with its regulatory functions and activities within the MS. This extends to the model type (discrete, centralised or decentralised) and to the relationships with other institutions providing regulatory services for medical products and technologies. The context should also specify what to implement in the QMS to support the NRA in handling and managing internal and external issues within its regulatory mandates and functions as well as meeting the needs and expectations of interested parties (i.e. customers and stakeholders).</td>
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<td><strong>Operation</strong></td>
<td>This chapter addresses the requirements for QMS implementation in core processes and activities which are within the mandates of NRA. It also provides guidance on documenting operational linkages of processes and systems for effective and efficient QMS implementation.</td>
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<td><strong>Performance evaluation</strong></td>
<td>This chapter provides recommendations regarding what should be implemented by the NRA to facilitate accurate, objective and efficient performance monitoring, analysis and evaluation of operations indicators, QMS effectiveness, resources and customer satisfaction.</td>
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<tr>
<td><strong>Improvement</strong></td>
<td>Requirements for NRAs to implement in the QMS to support continuous improvements based on collected, analysed and evaluated data.</td>
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5.1 Introduction

NRAs should have documented, available and accessible legislative laws and regulatory policies on medical products which describe the regulatory functions and activities that should be included in the QMS.

NRAs should list and maintain current versions and copies of national, regional and international management system standards and guidelines that are used for the QMS implementation.

NRAs should document the history and evolution of their QMS to demonstrate the controls and management of changes in the system to ensure that it is effective for the institution. The evolution and changes should be justified and related to any changes to the adopted national, regional and/or international management system standards and guidelines (e.g. the case of the East African Community’s Compendium of Quality Management System (QMS) Technical Documents for Harmonization of Medicine Regulation [5]).

NRAs should ensure that all existing and already implemented management systems are integrated in the QMS. The integration should ensure that there are systematic, adequate and appropriate linkages between the overall QMS and the management systems for specific technical or administrative functions. The QMS should be integrated into the business processes to ensure that it helps the NRAs achieve their legal mandates and functions.

The NRA should determine the functions and processes that are already covered by other management systems. This should be done to identify gaps and align specific management systems with the overall QMS of the NRA as much as possible to ensure consistency and facilitate effective performance monitoring and evaluation (M & E). The management systems for specific technical and administrative functions and processes are described in sub-chapters 6.5 to 6.10.
5.2 Scope of the QMS

This guideline aims to provide guidance on implementing a sustainable and effective QMS based on adapted ISO 9001 standard [2] requirements to address the needs of NRAs with respect to all regulatory functions, including administrative and supporting processes. The scope of the QMS should include functions, processes and the physical locations where they are undertaken.

NRAs should ensure that the implemented QMS provides a clear statement of scope that specifies the functions and processes that are covered as mandated by the national legal framework. The scope should include all applicable regulatory functions which are provided in the current version of the GBT [6]. In addition, the QMS should also cover all additional technical and administrative functions and processes that are part of the NRA’s routine operations.

Where there is more than one institution that is partially or fully involved in the regulatory activities of medical products of a country, the QMS for each institution should support consistency, effectiveness, efficiency and systematic collaborations to improve and strengthen coordination between institutions. The QMS should also include the technical and administrative functions and processes which are interrelated and interdependent for the effective undertaking of the affected regulatory function(s). The QMS should be clear on the scope for each involved institution to ensure that there are neither gaps nor overlaps of the processes and activities.

When a specific unit of an NRA has implemented a QMS (e.g. a quality control laboratory, inspectorate or province/zone/state), the scope should be clear on the inclusions and exclusions (with justifications as applicable) without weakening operational linkages and interdependencies for timely and effective regulatory decision-making. The scope statement of the implemented QMS should be documented and supported by relevant national legal framework and by current best practices of the affected functions and processes.
5.3 Organisational context of NRA

The NRA should demonstrate that it understands its organisational and operational context within the country’s regulatory framework as part of national health system. This understanding facilitates the identification and management of internal and external issues relevant to its ability to achieve the objectives as defined in the NRAs strategic plans.

The NRA should document the context in which it exists and in which it has been given the legal mandate to perform regulatory functions that are within the scope of the QMS. The context should indicate the limitations of the NRA and the relationships with other institutions which are part of its routine operations.

The documented context of the NRA should clearly indicate the technical and administrative areas which are not exclusively under the control and management of the NRA. This could include areas such as personnel recruitment, management of finances, procurement, and management of equipment and infrastructure.

Determination and documentation of internal and external issues should be integrated in the business processes of the NRA based on the needs and expectations of customers and stakeholders. The determination of internal and external issues should also be linked to the development of a strategic plan to ensure that the implemented QMS helps the NRA achieve the objectives.

Internal and external issues can change (e.g. changes to medical product acts or regulations, government restrictions on international travels or procurements, changes in national labour laws, or changes to professional practice regulations), and therefore they should be monitored and reviewed. The NRA should conduct and document reviews of its organisational context at planned intervals and whenever there are changes to the legal framework or when there are organisational or structural changes.

NRAs should understand the context as well as the internal and external issues that provide the foundation and inputs for determining a strategic plan, scope of QMS, quality policy, quality objectives and related risks and opportunities.
NRAs may use national legal provisions to identify different types of interested parties (customers and stakeholders) to the regulatory products and services that are provided. Where customers and stakeholders are defined in the national laws and regulations, this would be sufficient as long as it addresses all outputs and services provided by NRA. This identification helps NRAs to separate other stakeholders from customers who should also be the focus of the QMS. NRAs should focus on all interested parties that can affect its ability to achieve the quality objectives. In addition, these interested parties should be categorised along with those respective needs and expectations from the NRA that the implemented QMS is designed to support.

NRAs should have a robust and defined system in place to monitor, review and document the relevant requirements of interested parties at planned intervals.

NRAs should ensure that inputs and resources which are required to perform the processes and functions covered in the scope of the QMS along with expected outputs are determined, documented and provided. NRAs should document the sequences and interactions of the regulatory processes together with related measures and criteria for their control (e.g. key performance indicators (KPIs)). The level and type of controls which are applied to the regulatory processes should be determined and documented with a risk-based approach and should utilise the available opportunities. The QMS should provide procedures for evaluating the QMS processes and allow for the implementation of corrective actions under a controlled and managed change process. This should facilitate continuous improvements of the processes and the entire QMS.

The QMS should be integrated in the business processes to ensure that the personnel who are assigned with responsibilities and authorities in performing regulatory and administrative activities have the required competencies.
5.4 Leadership, management and organization

NRA TM should demonstrate leadership and commitment towards the effective implementation and sustainability of the QMS within the national legal framework through continual identification of the needs and expectations of its customers. The following are responsibilities of TM with respect to QMS:

a) Providing needed resources for the implementation of an effective QMS which is consistently implemented across the NRA units, functions and processes;

b) Integrating QMS requirements into the business processes and aligning the quality policy and quality objectives with strategic plans of NRAs;

c) Implementing a QMS which incorporates risk-based thinking and which is based on processes and functions rather than being built around individual personnel or specific activities;

d) Communicating the importance of QMS and conforming to the requirement to maintain consistency in NRA functions and to improve effectiveness and efficiency of QMS;

e) Engaging, supervising and supporting all NRA personnel to contribute to the implementation and effectiveness of the QMS and to ensure that the NRA achieves the intended expectations;

f) Reviewing the performance of the QMS and promoting improvements.

TM should ensure that the risks and opportunities that can affect the ability of the NRA to provide products and services of the quality expected by customers are determined and documented. TM should also ensure that NRA implements measures to enhance customer satisfaction. To increase customer satisfaction, innovation and best practices may be introduced into the NRA’s processes with the appropriate determination of related risks and practicality.

TM of NRAs should establish, implement and maintain a documented quality policy which contains actionable and practical statements that:

a) take into consideration the organisational context and strategic directions and plans and provide a framework for setting quality objectives;

b) include a commitment to comply with applicable national legislation as well as regional and global regulatory requirements and best practices;

c) include a commitment to continual improvement of the QMS.
The TM should ensure that the quality policy also includes a commitment to adopt and implement GRPs as provided in the *WHO Good Regulatory Practices: Guideline for National Regulatory Authorities for Medical Products* [3].

TM should communicate the quality policy to all NRA personnel and ensure that the personnel have read, understood and applied it within their respective activities. Where applicable and appropriate, controlled copies of the quality policy should be published and provided to customers and stakeholders through established document control procedures as per QMS requirements.

To effectively implement the QMS, TM should assign and document roles, responsibilities and authorities, and should ensure that this information is communicated and understood within the NRA. Depending on the organisational context of NRA and on the scope and complexity of the QMS, TM should assign the following responsibilities and authorities to one or more job function:

- a) ensuring that the QMS of the NRA conforms to the requirements of the adopted standards and guidelines;
- b) ensuring that the integrated QMS and business processes are delivering their intended results as per action and strategic plans of the NRA;
- c) monitoring and reporting on the performance of the QMS and proposing opportunities for improvements to TM;
- d) ensuring the promotion of customer focus throughout the NRA while assuring quality, safety and efficacy/effectiveness of health products;
- e) ensuring that the integrity of the QMS is maintained when changes (e.g. legislative, process, organisational or structural) to the QMS are planned and implemented.

TM should ensure that the job function(s) to be assigned the above responsibilities and authorities have the necessary competencies and have direct access and are accountable to TM.
5.5 Document and data management

NRAs should have guidelines, policies and procedures that are necessary for the effective implementation of the QMS within the legislative provisions.

QMS documents should include but are not limited to internally and externally generated hard copy and/or soft copy formats of regulations, drawings, policies, guidelines, strategic plans, action/work plans, manuals, procedures, registers, logbooks, databases, spreadsheets, templates and forms, codes of ethics and professional conduct, inventories, checklists and all other documents which are used in technical and administrative activities of NRAs.

QMS documents should include internally and externally generated evidential documents (e.g. records, files, and reports) in hard copy and/or soft copy formats which are retained by NRAs. NRAs should consider all published materials either on intranets or websites or in newsletters and other forms of publication to be part of QMS documents and covered by the requirements of this guideline.

Within the QMS, NRAs should implement policies and procedures for identifying, describing, formatting, reviewing, approving, controlling (e.g. distribution, access, retrieval and use), retaining and disposing of internally generated documents. QMS documents of external origin (e.g. regulations, standards, pharmacopeia and WHO guidelines) should be subjected to the same requirements as for those that are internally generated, to the extent possible and practical depending on the nature and intended use.

Where Information Technology (IT) is utilized to optimize business processes for technical and administrative functions, NRAs should ensure that the system templates, forms and software that are used are identified, reviewed, approved, controlled and maintained under the same QMS policies and procedures that apply for other documents.

NRAs should implement a data management, protection (i.e. confidentiality, loss and integrity) and retention policy/procedure to define clearly the types and categories of collected, analysed, evaluated and retained data. The policy/procedure should provide clear requirements for the format, medium and duration of retention for data and documents. In addition, there should be a policy/procedure for NRAs covering the maintenance and retention of all documents and data.
NRAs should plan and document how it will meet the needs and expectations of its customers and stakeholders as stipulated in the national legal mandates and regulations. The plan should include all technical and administrative functions, processes and activities of the NRA and their respective objectives.

When planning for the QMS, the NRA should consider the issues (internal and external) and requirements of the stakeholders and determine the risks and opportunities that need to be addressed in the context of the organization. The NRA should plan actions to address these risks and opportunities with assigned roles, responsibilities and authorities. The planned actions should include a framework for monitoring and evaluating the effectiveness of the actions taken. The NRA can choose the methods of risk management that suit its needs. Depending on the size, complexity and regulatory functions of the NRA, principles can be based on *WHO Guidelines on Quality Risk Management* [18] and ISO 31000 standard [19].

NRAs should establish quality objectives for relevant regulatory and administrative functions, for all levels and section of NRA and for all processes needed for the QMS. Where quality objectives are established for multiple levels within the NRA (e.g. directorate, department, unit or zone), the objectives should be consistent to ensure that all levels contribute towards achieving the overall expectations from legal mandates and of customers. The quality objectives should be integrated with business objectives to ensure that the QMS supports the consistency, effectiveness and efficiency of NRAs.

Quality objectives of NRAs should be consistent with its quality policy, should contribute to customer satisfaction, and should be relevant to the regulatory products and services as mandated by the national legal framework.

To the extent possible, quality objectives should be specific, measurable, attainable, realistic and time-bound (SMART). The QMS should provide the measures for NRA to communicate the objectives to designated audiences within NRA and the means to monitor and update the objectives.

QMS should include a plan to ensure that the set objectives will be met. The planning exercise includes determining the actions that will need to be taken, the resources that will be required (e.g. human and financial to purchase equipment and the required supplies), the responsibilities that will be assigned to staff for specific tasks, the timelines that will be defined for completion of each step and the means that will be used for monitoring and evaluating whether or not the objectives have been achieved.
The NRA should plan for changes to the QMS. The purpose of planning the change is to maintain the integrity of the QMS and ensure the NRA’s ability to provide conforming regulatory products and services during the change. For any change, the NRA should consider the availability of resources and necessary allocation or reallocation of responsibilities. This could be done by implementing an effective change management process within QMS. The need for changes can result from changing needs of customers and other relevant interested parties, for example, new products to be evaluated to grant market authorization, availability of new information and communication technologies (ICTs) for a service or process, a move to outsourcing of an important processes, departure of persons in key roles (e.g. due to retirement or job change), or a move to online service provision.

5.7 Support and resources

NRAs should determine and document resources which are needed to establish, implement, maintain and continuously improve the QMS. The determination should be done within the organisational context of the NRA and the scope of the legal mandates on the functions and activities. NRAs should also determine and document those technical and administrative resources which need to be provided by external providers (companies and individuals/experts).

NRAs should determine, provide and document the personnel and their required minimum competencies necessary for the effective implementation of the QMS and for the effective operation and control of its processes.

The competencies of the personnel should include a combination of appropriate education, professional training, experience and behavioural attitude as deemed necessary by the NRA. Where the assigned personnel with defined responsibilities and authorities do not have all the competencies, training plans should be developed and implemented with appropriate evaluation criterion for acquired competencies.

For consistency purposes of the QMS, NRA training plans for the rest of technical and administrative personnel and functions should be based on the competency framework or matrix and/or performance appraisal system coordinated by human resources departments. Records of evidence of an employee’s competence including diplomas or degrees, completion of training certificates, resumes, performance reviews, licenses and other documents should be retained.
The competency framework or matrix should be used in assigning official and non-official job function hierarchies and relationships (e.g. junior officer, senior officer, or head of unit). The framework should also include the procedure for designation or qualification of technical officers (e.g. Senior or Lead Assessor, Senior or Lead inspector, Senior or Lead Analyst); these should be supported by re-qualification procedures.

NRAs should determine, provide and maintain a documented list of infrastructures needed for technical and administrative processes in the execution of the legal mandates. Lists of the following should be maintained to allow for identification, location, type, quantities, versions, operational status (i.e. in use vs. not in use) and plans for qualification, validation, calibration, and maintenance (as applicable):

a) Buildings and associated utilities;
b) Technical (e.g., inspection and testing equipment) and administrative equipment (e.g., servers, computers, and printers), including hardware and software;
c) Transportation and logistical resources;
d) Information and communication technology.

NRAs should determine, provide and maintain the human and physical factors of work environment necessary for the operation of technical and administrative processes and activities within the context of organisational structure and national legislation. To the extent that it is practical, the environment should address social, psychological and physical (i.e. workspace) conditions to promote work-life balance. Depending on the activities of the NRA, applicable occupational, health and safety policies and procedures should be considered for implementation as provided in ISO 45001 Occupational Health and Safety [7].

NRAs and its units should implement and document a policy and procedure on the management of waste that is generated. The waste management should be conducted within the recommendations and applicable requirements of the current version of ISO 14001 [8].

NRAs should determine and document a list of monitoring and measuring resources and equipment used to ensure that the regulatory products and services meet the expected requirements. The equipment should be suitable for measurement activity to be undertaken and maintained to ensure continued fitness.

For the equipment including software that is used in technical measurements (e.g. inspection and laboratory equipment), NRAs should ensure that the results obtained from such equipment are valid and that the calibration of equipment is traceable to national or international measurement standards. The calibrated equipment should be identified with calibration status and safeguarded from adjustments, damage or deterioration.
In the event of measuring equipment found to be out of calibration, NRAs should evaluate and document the validity of previous measurement results obtained from the equipment and take appropriate actions.

The NRAs should consider how to determine and manage the organizational knowledge required to meet NRA’s present and future needs. Persons and their experience are the foundation of organizational knowledge. Capturing their experience and knowledge can generate synergies leading to the creation of new or updated organizational knowledge. In determining, maintaining and making organizational knowledge available, NRAs can benefit by a) learning from failures and successes, b) gathering knowledge from stakeholders, experts and partners, and c) capturing existing internal knowledge.

The tools for maintenance and distribution of organizational knowledge can include the intranet, libraries, awareness sessions, newsletters and others.

NRAs should ensure that all personnel (both full-time and part-time) have read and understood the quality policy and the relevant quality objectives that are relevant to their level in the organisation. This should be documented to verify that personnel understood their contributions to the effectiveness of the QMS and the benefits of improved performance. NRA personnel should be aware of the implications of not following policies and procedures established under QMS, for example, the release to customers of non-conforming regulatory products.

NRAs should determine, implement and document internal and external communication policies and procedures within the QMS. The policy should clearly describe “what” to communicate and define responsibilities and authorities for communication to the assigned competent personnel. Depending on the context, nature and intent of the communication, the policy should describe the level, audience and frequency of the communication including the format and medium (e.g. verbal, letter, mail, website, or intranet). Social media and mobile applications are additional tools for communicating with interested parties. The communication policy and procedure should be implemented within the legal framework of the NRA and related national (governmental) procedures and practices.
NRAs should ensure that planning of technical and administrative processes is done effectively as provided under 5.6 above for all operations within the scope of QMS.

NRAs should ensure that there is a process of consistent communication with customers and stakeholders to collect their feedback, inputs and other inquiries that may be useful in reviewing the requirements for the offered regulatory products and services. The details of the regulatory products and services offered including contingency requirements (such as those applied during natural disasters or epidemics) should be communicated upfront (e.g. through the NRA website, pre-submission meetings, or scientific advice) in order for customers to understand the information they need to provide to NRA relating to regulatory products and services.

NRAs should ensure that the requirements and expectations for the products and services are determined and defined within the applicable national laws and regulations. To promote public transparency and accountability, the product and service requirements may include fee schedules and delivery timelines for product market authorisations, licences, permits and certificates. This information may be included in the national guidelines and guidance notes and should be publicly available to customers and stakeholders.

NRAs should ensure through a review process that requests for services received from customers are complete and in conformity with service requirements. A checklist used for such reviews should be documented. When there is a difference between the requirements for products or services as requested by customer and the requirements prescribed by NRA, the same should be communicated to the customer and resolved before processing the request. Any verbal request or change in the requirements, either by the NRA or by the customer, should be confirmed before service is processed.

When the requirements for products and services are changed due to any reason, NRAs should take measures to inform all relevant interested parties. NRAs should retain evidence of the results of the revisions to the requirements of products and services and any new requirements for the products and services that are provided.
When NRAs plan on implementing new regulatory function(s) due to the revision of the national legal framework or wish to introduce new regulatory products and/or services (such as through mobile phone application), the following process steps should be followed:

a) Determine and document the process(es) that will form part of the new function including the stages, steps and control measures needed through implementation roadmaps or projects. The determination should include expected reviews, verifications and validations that the processes are robust enough for the intended function. NRAs should also determine and document the competencies, responsibilities and authorities of the project development team. Where the NRA would not be able to provide all the required resources, the NRA should document those resources that hat will be externally sourced. NRAs should determine the need to involve customers, stakeholders and internal personnel to ensure that key inputs are collected. NRAs should also assess whether any of the existing requirements (e.g. timelines or schedule of fees) are applicable to the new regulatory function or whether there is a need to establish new ones. All documents used and generated out of these roadmaps should be retained in an appropriate format and medium.

b) Once the implementation roadmap has been completed, NRAs should determine and document the inputs such as performance indicators, national legal requirements for compliance, and codes of ethics and professional conduct, as well as the potential consequences of failure using a risk-based approach.

c) As defined in the implementation roadmaps, intermediate reviews (where practical and possible), verification steps (i.e. comparing the new application/process with a similar proven application/process) and validation exercises (i.e. testing under intended user conditions) should be conducted by NRAs to ensure that the resulting function or product meet the requirements for the intended use.

d) The expected outputs of design and development process will be in the form of standard operating procedures (SOPs) or service provision manuals that give the information necessary for all the processes required to provide intended products and services including information to be provided by the customers.

e) Where changes are to be made in the new application or to the developed products or process(es), these changes will be identified, reviewed and controlled. A risk-based change management procedure should be documented and implemented.
NRAs should ensure that externally provided products and services (e.g. subcontracted ICT support, purchased reference standards, or subcontracted quality control laboratory testing) required for technical and administrative functions and activities of the NRA, conform to the QMS requirements. Where national laws and regulations exist for managing use of public NRA funds in procurement, for example, a national public procurement Act with procedures based on amount thresholds for either single sourcing or open/closed bid competitions and decision levels (i.e. Director General, Council, or Board level), the QMS should not duplicate any procedures which are provided for public procurements; however, the NRA should ensure that the public procurement procedure conforms to the requirements given in the subsequent paragraphs below and should close gaps, if any. The NRA should also implement these requirements when it carries out direct procurement.

NRAs should ensure that competence criteria are defined, documented and implemented for the evaluation, selection, performance monitoring, and re-evaluation of external providers and suppliers (e.g. NRAs having documented, well-defined and transparent criteria for the selection and performance monitoring of external non-staff experts).

When NRAs must perform in-house pre-qualification of providers, there should be a documented procedure and policy on the competence criteria for evaluation, selection, performance monitoring, and re-qualification. The pre-qualification and re-qualification should focus on the competence of the individual persons and the institution or company to provide the products and/or services that meet applicable QMS requirements.

NRAs should implement measures for ensuring that the externally provided products and services do not adversely affect the organisation’s image and ability to consistently deliver the products and services to the customers.

The NRA should determine which specific controls are to be implemented for an external provider and for incoming products and services provided by them. Control activities that may be considered include inspections, certificates of analysis or testing, second party audits, evaluation of statistical data and KPIs.

NRAs should clearly communicate the requirements and controls to be applied to the external provider and both parties should agree as to what is required. This understanding of requirements is usually reflected in a technical service agreement or through a purchase order or contract. The NRA should ensure that the requirements communicated to the external providers are complete, clear and address any potential issues.
NRAs should carry out their technical and administrative functions for processing of requests for services under controlled conditions. The controlled conditions should include, as applicable:

a) Use of guidelines, policies and procedures that provide the requirements for the regulatory products and services including those for performance of activities.

b) NRAs should document and implement measures for reviewing (peer review or QA review), approving and releasing of output of intermediate processes to ensure that there are adequate controls for those activities that are involved in providing conforming products and services. For this purpose, the following guidelines should be considered for adoption and implementation as applicable and to the extent necessary:


   Where the NRA has a unit or site responsible for GxP inspections, recommendations and technical requirements: *WHO Quality Management Systems Requirements for National Inspectorates* [12].

c) As required, monitoring and measuring resources and equipment should be available and in use to ensure that the processes are effective and controlled. Where measuring equipment must be used in providing regulatory services of the NRA laboratory, technical requirements and recommendations from the following guidelines should be considered for adoption and implementation as applicable and to the extent necessary: *WHO Good Practices for Pharmaceutical Quality Control Laboratories* [13] for physico-chemical and *WHO Good Practices for Pharmaceutical Microbiology Laboratories* [14] for microbiological testing. These two WHO guidelines can be supported and complemented with current *ISO 17025 standard* [15] and *EDQM, Quality Management Documents* [16].

d) NRAs should ensure that the provided infrastructure and working environment are suitable for the operation of both technical and administrative processes and activities and for the performance of applicable regulatory functions.

e) NRAs should ensure that the appointment of personnel is based on the required competencies and qualifications and is described and documented in respective units. This should include the implementation of control measures to avoid or reduce human errors through peer and QA reviews.
NRAs should document and implement policies and procedures on the unique identification and traceability of released regulatory products and services. As far as practical and possible, these also should be supported by systematic measures to facilitate traceability of the products and services to the equipment, software, personnel and location used by the NRA.

NRAs should implement measures to verify, protect and safeguard properties that belong to customers and stakeholders, including providers, and avoid their loss, damage and any effects that would make them unsuitable for use. This can include properties, for example, that may have been seized and quarantined or used as input for making regulatory decisions. Examples of property include marketing authorization product dossiers, quarantined products, samples for testing, intellectual property or personal data.

The NRAs should determine those products and services (e.g. seized drugs, drug samples collected for analysis, vaccines under release, licences, market authorisations, permits or certificates to be issued) that can deteriorate or degrade and implement appropriate preservation methods.

NRAs should document and implement practical procedures on release of regulatory products and services through all stages up to and including the customer. The release process includes defining responsibilities and authorities of the involved job functions. These processes should provide an internal QA procedure to ensure that the released products and services comply with all planned requirements.

NRAs should document and implement procedures for control of non-conformances and deviations that are observed or reported. Control actions include correcting the non-conformity or releasing product under suspension of due authorization. If the nonconformity is discovered after the product has been delivered to the customer, the NRA should take appropriate actions to prevent unintended use or undesired consequences and take measures such as issuing a recall or suspension. The QMS should not duplicate any existing procedures in technical units such as a laboratory or inspectorate.
5.9 Performance evaluation

NRAs should conduct monitoring, measurement, analysis and evaluation of all planned technical and administrative activities to determine whether the intended results, as defined in action plans, work plans or strategic plans, are being achieved. NRAs should define what needs to be monitored and measured (e.g. characteristics of processes, products, services and potential risks) and the methods to be used for monitoring, measurement, analysis and evaluation of the performance and effectiveness of the QMS. The monitoring, measurement, analysis and evaluation of the NRA performance should be linked to the planned KPIs (or simply indicators) as applicable. The establishment and implementation of the indicators should be as practical as possible to ensure that value is added through monitoring, measurement, analysis and evaluation activities. Therefore, the indicators or KPIs should have clear, relevant, economic, adequate and monitorable (CREAM) attributes. NRAs should determine and document the frequency of M & E of the indicators from the implemented action and activity plans as well as from the performance and evaluation of the QMS. NRAs should ensure that the M & E framework is consistent across different units, levels and functions of the organisation. The framework should be documented and aligned with the relevant quality objectives (strategic objectives) of the NRA.

The NRA should develop methods to seek feedback from a selected population of customers or from every customer at the end of a service provision. Means to obtain feedback is provided by social and published media such as web sites and message boards, opinion surveys and compliments or complaints. The NRAs should determine the degree of customer satisfaction after the results of feedback are analysed and evaluated and then act based on this information. NRAs should document, implement and publish comprehensive policies and procedures on handling of complaints in order to provide guidance to customers and stakeholders on complaint submission, investigation, resolution, appeal and communication within the national legal provisions. The procedures should define roles and responsibilities of a complainant and the NRA and specify timelines to effectively manage complaints related to regulatory products and services.
NRAs should analyse and evaluate monitoring and measurement data and information to determine summary performance results of the following:

a) Compliance of regulatory products (e.g., guidelines and software applications) to quality and validity requirements;

b) Compliance of regulatory services to quality and timeline commitments and requirements;

c) Degree of customer satisfaction;

d) Performance and effectiveness of the QMS for the overall NRA and/or the QMS for NRA units or functions and the need for improvements to the QMS;

e) Level of implementation of action or activity plans and strategic plans at the time of reporting;

f) Effectiveness of the actions taken to address risks and opportunities (such as strengths, weaknesses, opportunities and threats (SWOT) analysis);

g) Performance of external providers (including external technical experts).

NRAs should plan and conduct internal audits (at least once a year) to verify compliance to the QMS requirements across the organisation and to verify that the QMS is effectively implemented and maintained. An internal audit programme should have defined planning requirements, frequencies, methodologies, responsibilities, competencies and reporting. Each internal audit programme should take into consideration the importance and associated risks of the processes to be audited, the internal and external changes affecting the NRA, and the results of previous audits in order to:

a) Define the audit requirements for the criteria (QMS requirements) of compliance, scope (functions and departments to be audited) and methodology (interviews, examination of records, results, and trends) for each audit. The criteria for compliance may add and implement a scale for reporting observations (critical, major and minor) which should be clearly and objectively defined within the internal audit programme.

b) Select appropriately qualified and competent auditors who can conduct the audit objectively and impartially. The impartiality can be achieved by employing auditors that audit those processes in which they were not involved while serving in the NRA.

c) Ensure that the internal audit reports are submitted to TM for actions.

d) Take appropriate corrections and corrective actions without delay and within timelines defined by TM. Where corrective actions are delayed due to unavailability of required resources, appropriate risk management plans should be implemented and documented.

e) Retain records of internal audit programmes and internal audit reports including records of corrections and corrective actions.
Further technical guidance on managing internal audits can be adopted from the current version of ISO 19011 [17].

TM of NRAs should review the QMS at planned intervals (i.e. at least once a year) to ensure its suitability, adequacy, effectiveness and alignment with the strategic direction of the organisation as per strategic plans. Ideally, TM should review the QMS alongside the review of NRA’s business plans (activity, action or strategic plans). This will ensure that the QMS remains integrated into business processes effectively.

QMS reviews should consider inputs as provided in table 2 with the listed expectations of the outputs to come out in the minutes of the meeting (report).

**Table 2: Inputs and outputs for review meetings**

<table>
<thead>
<tr>
<th>Inputs (to be reviewed)</th>
<th>Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status of actions from previous reviews.</td>
<td>• Decisions and actions related to opportunities for improvements.</td>
</tr>
<tr>
<td>Changes in internal and external issues which are relevant to the QMS.</td>
<td>• Decisions and actions related to changes required to the QMS.</td>
</tr>
<tr>
<td>Information on performance and effectiveness of QMS, including trends in:</td>
<td>• Actions on additional resources needed to implement improvement initiatives and suggested changes in QMS and in other areas where resources (including human resources) are not adequate.</td>
</tr>
<tr>
<td>1. Customer satisfaction and feedback from stakeholders;</td>
<td>• Actions to implement for quality objectives achievement.</td>
</tr>
<tr>
<td>2. Extent to which quality objectives have been achieved;</td>
<td>• Responsibilities for follow up of actions on the decisions taken in the meeting.</td>
</tr>
<tr>
<td>3. Performance on compliance to commitments and requirements for regulatory products and services;</td>
<td>• Management review meeting minutes to be retained as records or reports and communicated appropriately to internal and external customers and stakeholders as per NRA communication policy.</td>
</tr>
<tr>
<td>4. Non-conformances and deviations, and status of implemented corrective actions;</td>
<td></td>
</tr>
<tr>
<td>5. Results of M &amp; E of indicators/KPIs;</td>
<td></td>
</tr>
<tr>
<td>6. Results of internal and external audits;</td>
<td></td>
</tr>
<tr>
<td>7. Performance of external providers (including external technical experts).</td>
<td></td>
</tr>
<tr>
<td>Adequacy of resources (financial, human, equipment and infrastructure).</td>
<td></td>
</tr>
<tr>
<td>Effectiveness of the actions taken to address risks and opportunities (such as SWOT or similar analysis).</td>
<td></td>
</tr>
<tr>
<td>Opportunities for improvements of QMS.</td>
<td></td>
</tr>
</tbody>
</table>
Management review agenda (inputs) and meeting minutes should be retained as records or reports and communicated appropriately to internal stakeholders as per NRA communication policy.

5.10 Improvement

There are different methods to conduct improvement, such as correcting existing nonconformities and deviations and taking actions to prevent recurrence, or conducting ongoing, small-step improvement activities based on opportunities identified either through risk analyses or breakthrough projects. These improvement activities can lead to innovation, to revision and/or improvement of existing processes or to the implementation of new processes. NRAs should implement and document measures to record and react to non-conformances and deviations by taking actions to control and correct them, including with related plans for managing related activities, if any. In addition, NRAs should conduct a root cause analysis (RCA) and evaluate the need to act in order to avoid recurrence of the non-conformances and deviations in the affected area as well as in any similar processes in the organisation in which such non-conformances or deviations could occur.

The steps involved in this process are:

a) Reviewing and analysing the non-conformance or deviation;

b) Determining, to the extent possible, the cause(s) of the non-conformance or deviation;

c) Determining if similar non-conformances exist or could potentially occur within the affected unit or function and/or other NRA units or functions having similar processes.

After implementing the corrective action, NRAs should review and document the effectiveness of the corrective action taken through practical means including during future internal audits which look for a recurrence of the same non-conformity. The results of the RCA and the implemented corrective actions should be used to update the risk and opportunity planning as applicable. Where corrective actions lead to changes to the process(es), NRAs should plan for similar changes to the QMS supported by a defined change management plan. NRAs should define the communication of non-conformances and corrective actions reports to internal and external customers as defined in the communication policy/procedures.

For technical and administrative processes, NRAs should ensure that the handling of conformances, deviations and corrective actions is consistent across the entire organisation. Non-conformances and deviations that are related to professional misconduct of NRA personnel should be handled in accordance with conditions of employment and service including related national legal provisions.
Improvement can include actions to reduce process variation, increase consistency of process outputs, products and services, and improve process capability. This should be done to enhance the NRA’s performance and give benefits to its customers and stakeholders. The results from performance monitoring and evaluation and management reviews should be used to decide which continual improvement actions should be implemented and what resources and support should be provided for their implementation by TM.

6 QMS IMPLEMENTATION METHODOLOGY

Full commitment of the head of NRA and the heads of technical, support, and /administrative units (i.e. TM) is necessary for effective implementation and maintenance of the QMS in NRAs. This commitment should be supported by demonstrating leadership, management, commitment and customer focus through all stages of the implementation of QMS. The QMS should be designed to be integrated in business processes (i.e. not stand alone), supported with adequate resources (human, financial, equipment and infrastructure) and created to be simple enough to remain manageable with the available resources while being effective enough to support consistency, effectiveness and efficiency.

Potential mechanisms that can help in QMS implementation:

- Establishing strong coordination and communication mechanisms;
- Receiving high level support from TM for QMS implementation;
- Establishing high level ownership and commitment by TM for QMS implementation and maintenance;
- Including QMS implementation roadmaps in NRA strategic plans by TM when submitting to an oversight body (Council, board, committee or MOH) for approval as applicable;
- Including QMS implementation in NRA in the national health strategic plans;
- Including responsibilities and authorities for contributing to QMS in every staff job description and human resources (HR) performance appraisals;
- Creating and implementing training plans for QMS personnel based on NRA competence frameworks;
- Engaging all customers and stakeholders for communication and awareness;
- Implementing applicable ICT tools for internal and external implementation of QMS and communication of quality policy awareness;
- Imbedding assigned QMS personnel within business processes with dual responsibilities of business job functions and QMS responsibilities to support and maintain the QMS in the respective business unit.
Regardless of the size of NRA, the scope of regulatory functions and the NRA organizational model (i.e. discrete, centralised or decentralised), the recommendations in Appendix 1 for gap and situational analyses should be considered when implementing QMS and when planning for continuous improvement of a QMS that is already implemented. NRAs should first identify existing gaps and determine the level of implementation of the QMS with the use of Appendix 1 and self-benchmarking results.

Appendix 1 has categorised the key aspects of the QMS as:

a) **Non-existing QMS**: NRAs should focus on ensuring that processes and activities are performed consistently regardless of the personnel or location of execution. This may be covered for certain areas with automated systems (such as laboratory information management systems (LIMS) for laboratories or e-Performance appraisals for HR). NRAs should prioritise development and implementation of procedures for areas based on the related risks with respect to the products and services, the affected quality objectives and the availability of resources for maintenance of the procedures. This means that not every area should be prioritized at the same time for QMS development and implementation (for NRAs without implemented QMS).

b) **Existing QMS without implementation**: The focus at this stage should be on ensuring that consistent procedures are developed and implemented for the QMS to support business processes effectively. Careful consideration should be given at this stage to objectively addressing the activities for gap identification and validation; these steps would also be useful for NRAs that have already developed and implemented QMS. NRAs should ensure that the person(s) identifying the gaps have necessary competence and that TM fully supports the process. The review should be done to cover all areas in which the QMS has been implemented and the scope should be limited to records, reports or other means of verification that procedures have been implemented and are being used to the full extent as intended. The outcome of this review should be a RCA with proposed measures to implement; these measures should take into consideration of the availability of resources and associated risks of delayed implementation.

c) **Ineffective QMS**: Addressing this stage is considered useful once the first two stages are addressed for the respective processes and activities. This stage focuses on the main objectives of the QMS, namely, to ensure that the NRA is being effective in supporting business processes and activities, providing regulatory products and services, and achieving strategic objectives. Therefore, it is important that QMS is simple and manageable enough in its implementation and maintenance to avoid diverting NRA time and resources on QMS instead of delivering regulatory products and services to the customers as provided by national legal mandates. Increasing effectiveness and efficiency of the QMS may also involve the adoption and implementation of IT to remove human errors while promoting consistency, reducing time for implementation and recording, and providing long-term cost reductions.
6.1 Gap analysis for developing a roadmap for QMS Implementation

The information in table 3 can be used to identify gaps and to define activities to be done for QMS implementation based on the recommendations of the guideline. The planning, prioritisation and implementation should be as practical as possible and be determined by the NRA taking into consideration the availability of resources and priorities for the provision of regulatory products and services.

Table 3: Gap analysis

<table>
<thead>
<tr>
<th>Guideline chapter</th>
<th>Existing system</th>
<th>Stage 1 (non-existing QMS)</th>
<th>Stage 2 (existing QMS without implementation)</th>
<th>Stage 3 (ineffective implementation of QMS)</th>
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<tbody>
<tr>
<td></td>
<td>Linking and integration of overall QMS to quality systems and (automated) software for:</td>
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<tr>
<td>Introduction</td>
<td>NRAs should perform an organisational wide review for consistency of practice by different staff using the same processes and the existing system. This review can be used to identify a consistency gap for QMS intervention and document development. Once the reviews are completed and gaps established, reviews should be done to determine if the existing systems and/or software have operational interfaces between one another when they all contribute towards achieving the same objective; these reviews can help to identify operational gaps in interfaces. QMS should be used to link the processes and activities between systems and/or software by providing documents.</td>
<td>Where consistency and operational interfaces have been implemented and supported under QMS, NRAs should conduct reviews to identify gaps in the level of implementation of the QMS documents. This should be evaluated by reviewing records and reports generated from the systems and/or software to establish consistency and operational linkages for same objectives. Where gaps are found to exist, NRAs should perform RCA and implement changes as appropriate to stage 1 QMS interventions.</td>
<td>NRAs should conduct reviews to identify gaps in effectiveness and efficiency of the QMS interventions with respect to the achievement of the intended objectives based on evidence from stage 2 outputs. When gaps have been identified, NRAs should revise the QMS implementation documents to ensure that they are effective and efficient in contributing towards the achievement of the objectives.</td>
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<td></td>
<td>- Registration and market authorisation</td>
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<td>- Laboratory</td>
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<td>- Inspections and licensing</td>
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<td>- Vigilance</td>
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<td>- Market surveillance and control</td>
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<td>- Clinical trials oversight</td>
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<td>- Lot release</td>
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<td></td>
<td>- Environmental (waste) management</td>
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<td>- Occupational health and safety</td>
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<td>- Finance and accounting</td>
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<td>- e-Procurement</td>
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<td>- Planning, monitoring and evaluation</td>
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<td></td>
<td>- Human resource performance appraisal, training and staff/talent retention</td>
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<tr>
<td></td>
<td>- others</td>
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<tr>
<td>Scope of the QMS</td>
<td>Documented statement defining the scope of the regulatory functions, physical locations, processes, regulatory products and services of the NRA</td>
<td>To identify gaps in scope of QMS, NRAs should review for the existence of consistent documented scope statements which includes all areas, locations and processes.</td>
<td>NRAs should review the level of implementation of the QMS across all units (including administrative) and locations to identify gaps in the implementation of the scope.</td>
<td>When identifying gaps for QMS revision, NRAs should review the effectiveness and efficiency of the scope of QMS in facilitating the provision of required products and services</td>
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<tr>
<td>Organisational context of NRA</td>
<td>Adequate description and mandates of NRAs in terms of:  * ability to define internal and external issues and customers and stakeholders</td>
<td>NRAs should review and identify gaps in the consistency of how issues for planning are determined among different units of the organisation. QMS documents should be developed and implemented to establish consistency.</td>
<td>NRAs should review the planning reports and records from different units to identify gaps in implementation of QMS documents. Where gaps are identified, RCA should be performed to ensure that procedures are implemented.</td>
<td>NRAs should review the contribution of QMS documents in making the planning to be more effective and efficient to identify gaps. Identified gaps should be addressed by implementing changes to QMS documents.</td>
</tr>
<tr>
<td>Leadership, management and organization</td>
<td>Adequate description and mandates of NRAs in terms of:  * ability to develop and implement organisational structure  * ability to develop and implement quality policy and customer focused initiatives  * ability to assign QMS responsibilities and authorities to personnel</td>
<td>NRAs should review the consistency of supervisory and reporting structures, consistency in developing and implementing quality objectives, and consistency of assigned QMS responsibilities and authorities across units and locations to identify gaps in leadership, management or organisation. QMS procedures should be implemented to ensure that leadership, management and organisation processes are done consistently in implementation of QMS.</td>
<td>NRAs should review the level of implementation of existing QMS procedures to ensure consistency in organisational structures, job titles, reporting lines, quality policies, QMS responsibilities and authorities across the units and locations to identify gaps in implementation of procedures. RCA should be done to determine changes that would improve implementation levels of QMS procedures.</td>
<td>NRAs should review the effectiveness and efficiency of the procedures in supporting leadership, management and organisation processes to identify gaps in existing QMS. Procedures should be revised to ensure that they are effective and efficient in supporting NRA and all its units in having leadership, management and organisation that is able to deliver on the regulatory products and services.</td>
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<tr>
<td>Document and data management</td>
<td>Documents under the QMS that are internally generated or from external origins for:  * Regulations  * Guidelines  * Policies  * Notes and guidance  * Procedures (SOPs/Work instructions)  * Lists, Registers, Logbooks  * Databases and spreadsheets  * Templates, Forms  * Application documents (dossiers, files)  * Financial, accounting.</td>
<td>NRAs should identify gaps by reviewing the consistency in the development, review, approval, version and access control, distribution, storage, retrieval and disposition of documents as applicable across all units and locations of the organisation. Where gaps exist, procedures should be implemented to ensure that documents are managed consistently across all units and locations of the NRA.</td>
<td>NRAs should review the records in units and locations to identify gaps in the implementation of existing procedures for management of documents. RCA should be done to determine measures to promote implementation of existing procedures.</td>
<td>NRAs should review the effectiveness and efficiency of the procedures in identifying gaps in the management of documents. Procedures should be revised to ensure that they are more effective and efficient in the management of documents of the NRA. NRAs can consider the use of IT in the management of documents depending on the availability of resources, size of NRA and complexity of documents to be managed.</td>
</tr>
</tbody>
</table>

RCA = root cause analysis
| Planning                          | Linking and integration of planning in quality systems and (automated) software for objectives in:  
|                                 | - Technical activities  
|                                 | - Support and administrative activities  
|                                 | - Monitoring and evaluation  
|                                 | NRAs should review the consistency in the planning, monitoring and evaluation of technical, and administrative, and support activities with associated risk and change management plans to identify gaps across all units and locations. QMS procedures should be implemented to ensure that all planning, monitoring and evaluating of technical and support activities are done consistently and with related risk and change management plans.  
|                                 | NRAs should review the level of implementation of procedures for consistency in planning, monitoring and evaluating of technical and support activities. To identify gaps for QMS revision, the review should evaluate the consistency in implementation of risk and change management plans based on existing records and reports. RCA should be done to ensure that procedures are implemented.  
|                                 | To identify gaps with existing procedures, NRAs should review the effectiveness and efficiency of the QMS procedures in support of planning, monitoring and evaluating of activities, risks and changes. QMS procedures should be revised or replaced with automated systems based on the complexity and size of the NRA and its planning activities.  
| Support and resources           | Adequate and quality resources for:  
|                                 | - Personnel and competencies  
|                                 | - Organisational knowledge management  
|                                 | - ICT  
|                                 | - Work environment  
|                                 | - Communication and awareness  
|                                 | NRAs should review the consistency in the allocation of personnel, training in QMS, knowledge sharing, use of ICT and communication of QMS requirements to identify gaps for QMS implementation. Procedures should be implemented to ensure consistency across all units and locations in allocation of personnel, training of staff in QMS implementation, use of intranets and other ICT tools and communication.  
|                                 | NRAs should review the records to identify gaps in levels of implementation of existing procedures for QMS personnel, competencies, knowledge management, ICT, work environment and communication across all units and locations. RCA should be done to ensure procedures are implemented.  
|                                 | To identify gaps for QMS revisions, NRAs should review the effectiveness and efficiency of the procedures in ensuring that there are adequate and quality personnel, QMS competencies, knowledge management, ICT, workspace, communication and awareness of QMS implementation. Procedures should be revised to ensure that they are effective and increase efficiency in their implementations.  
| Operation                       | Process approach focused on the regulatory products and services and on NRA quality objectives  
|                                 | To identify gaps for QMS implementation, NRAs should review the consistency in the conduct of technical and administrative activities in providing products, services, and operational interfaces or linkages among processes that contribute to the same product, service or quality objective. Where gaps exist, procedures should be implemented to ensure consistency and operational linkages of processes.  
|                                 | NRAs should review the records from technical and administrative units and locations to identify gaps in the implementation of existing procedures. RCA should be performed, and measures should be put in place to ensure full implementation of procedures across all affected units and locations.  
|                                 | NRAs should review and identify gaps in the effectiveness and efficiency of the implemented procedures and quality systems in facilitating the provision of products and services that meet requirements and support the achievement of the objectives. Procedures and systems should be revised to ensure that they are effective and increase efficiency in the processes for providing products and services and for supporting the achievement of NRA objectives.  

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<table>
<thead>
<tr>
<th>Performance evaluation</th>
<th>NRAs should review and determine gaps in consistency in the M &amp; E activities across all units and locations for QMS implementation. Where gaps in consistency are identified, procedures should be implemented to ensure that all M &amp; E of performance indicators are done consistently across different units and locations of NRAs.</th>
<th>NRAs should review and identify gaps in the level of implementation of existing procedures and systems of the QMS for the M &amp; E framework. RCA should be done to inform revised measures for the implementation of procedures and systems across all affected NRA units and locations.</th>
<th>NRAs should review and identify gaps in the effectiveness and efficiency of the implemented QMS procedures and systems used for M &amp; E. These procedures and systems should be evaluated to ensure that their output provides evidence useful for planning of continuous improvements. Where gaps exist, NRAs should revise the procedures and systems to ensure that they are more effective and efficient in supporting M &amp; E of performance indicators across all units and locations of the organisations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>NRAs should review and identify gaps in the consistency of handling and prioritisation of improvements across the entire organisation. Where there are inconsistencies, procedures should be implemented to ensure that all proposals for improvements are submitted with evidence and evaluated with respect to priorities and availability of resources. Procedures for improvement should define responsibilities and authorities for handling, planning and implementation of improvements.</td>
<td>NRAs should review and identify gaps in levels of implementation of QMS procedures for handling and implementing improvements across all units and locations of the organisation. Where gaps are identified, RCA should be done with revised measures for the implementation of the procedures.</td>
<td>NRAs should review and identify gaps in the effectiveness and efficiency of the procedures in facilitating timely implementation of improvements. Procedures should be revised to ensure that they are more effective and efficient in facilitating timely implementation of improvements.</td>
</tr>
<tr>
<td>Evidence based improvements</td>
<td>NRAs should review and identify gaps in the consistency of handling and prioritisation of improvements across the entire organisation. Where there are inconsistencies, procedures should be implemented to ensure that all proposals for improvements are submitted with evidence and evaluated with respect to priorities and availability of resources. Procedures for improvement should define responsibilities and authorities for handling, planning and implementation of improvements.</td>
<td>NRAs should review and identify gaps in levels of implementation of QMS procedures for handling and implementing improvements across all units and locations of the organisation. Where gaps are identified, RCA should be done with revised measures for the implementation of the procedures.</td>
<td>NRAs should review and identify gaps in the effectiveness and efficiency of the procedures in facilitating timely implementation of improvements. Procedures should be revised to ensure that they are more effective and efficient in facilitating timely implementation of improvements.</td>
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</tbody>
</table>
The QMS roadmap for NRAs will depend on the respective stages of implementation. The roadmap will be used to identify activities to be done, required resources, competencies of personnel, responsibilities and authorities, timelines (timeframe) and prioritisation based on the needs of the NRA with respect to the regulatory products and services as mandated by national laws and regulations. Table 4 summarises the steps in the development and implementation roadmap for QMS.

Table 4: Development of QMS implementation roadmap

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<thead>
<tr>
<th>Steps</th>
<th>Activity</th>
<th>Responsible</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Assign resources (personnel, financial, equipment and infrastructure).</td>
<td>TM</td>
</tr>
<tr>
<td>2</td>
<td>Use Appendix 1 and results from self-benchmarking to determine the status of the QMS and submit report to TM, noting activities and areas that require actions.</td>
<td>Assigned staff/Consultant</td>
</tr>
<tr>
<td>3</td>
<td>Prioritise activities based on availability of resources (internal and external), risks of non-implementation and regulatory products and services as mandated by national laws and regulations.</td>
<td>TM</td>
</tr>
<tr>
<td>4</td>
<td>Allocate responsibilities and authorities with timelines for development, review, approval, implementation, M &amp; E of prioritised QMS requirements.</td>
<td>TM &amp; Assigned staff/Consultant</td>
</tr>
<tr>
<td>5</td>
<td>Validate the prioritisation of QMS requirements, timelines, responsibilities and authorities with NRA staff through collection of input and feedback to promote ownership of QMS implementation.</td>
<td>TM &amp; Assigned staff/Consultant</td>
</tr>
<tr>
<td>6</td>
<td>Consolidate the feedback and input into an activity/action plan as a roadmap for QMS implementation for the NRA.</td>
<td>Assigned Staff/Consultant</td>
</tr>
<tr>
<td>7</td>
<td>Integrate the QMS roadmap (activity/action plan) into the NRA organisational activity/action plans, the NRA strategic plans and the MOH health strategic plan/policy as applicable.</td>
<td>TM</td>
</tr>
</tbody>
</table>
## Appendix 1: Activity plan for QMS implementation with effectiveness and performance indicators

<table>
<thead>
<tr>
<th>Step</th>
<th>Activity</th>
<th>Ref sub chapters</th>
<th>Effectiveness and performance indicators</th>
<th>Responsibility within the NRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Appointment of QMS focal person(s or lead(s))</td>
<td>6.4</td>
<td>Official letters of appointment with defined responsibilities and authorities in QMS</td>
<td>Head of the NRA</td>
</tr>
</tbody>
</table>
| 2.   | QMS focal person(s) understand the QMS requirements | 6.4 & 6.7 | • Competency matrix for QMS focal person(s)/lead(s)  
• Training plans for competency gaps in QMS implementation  
• Training records of QMS focal person(s)/lead(s)  
• Training/orientation records in development and implementing QMS documents (Quality manual, SOPs and/or forms and templates) | TM |
| 3.   | QMS focal person(s)/lead(s) conducts a gap analysis of current system based on tables 3 and 4 of the guideline and develops a QMS action plan (as part of strategic plan) | 7.1 | • Documented gap or situation analysis report  
• Documented roadmap with resources, timelines and responsibilities (part of NRA strategic and action plans) | TM  
• QMS focal person(s)/lead(s) |
<p>| 4.   | QMS focal person(s)/lead(s) conducts orientation and awareness sessions for NRA employees on QMS development and implementation (with roles and responsibilities) | 6.7 | Accessible and available QMS orientation and awareness sessions records and materials in appropriate format | QMS focal person(s)/lead(s) |</p>
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<tr>
<td>5.</td>
<td>• Establishment of NRA current context (SWOT analysis), if already available.</td>
<td>6.1, 6.2 &amp; 6.3</td>
<td>• Documented official organisational chart covering NRA governance and TM and internal and external operational relationships</td>
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<td></td>
<td>• Determining comprehensiveness of the legal provisions (Acts and regulations) in describing interested parties relevant to QMS</td>
<td></td>
<td>• Documented description of internal and external issues including SWOT analysis of the NRA (with defined customers and stakeholders based on legal provisions)</td>
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<td></td>
<td>• Identification of QMS processes, sequences, linkages and interdependencies</td>
<td></td>
<td>• Documented description of internal and external customers and stakeholders with their respective needs and expectations (if not adequately described in the national legislations)</td>
</tr>
<tr>
<td></td>
<td>• Determining scope of QMS and relationships of its processes</td>
<td></td>
<td>• Documented statement of scope for the QMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Documented flowcharts, process maps and their operational linkages for all processes under the scope of QMS with related products and services</td>
</tr>
<tr>
<td>6.</td>
<td>Documenting Quality Policy within the context and strategic direction of NRA</td>
<td>6.4</td>
<td>Documented, accessible (publicly), and available quality policy understood by NRA staff</td>
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<td>• TM</td>
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<td>• QMS focal person(s)/lead(s)</td>
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<tr>
<td>7.</td>
<td>Use information from step 5 above, as input, to determine risks and opportunities and develop risk and opportunity management plans</td>
<td>6.6</td>
<td>• Documented and controlled registry of assessed and categorised risks and opportunities (from SWOT analysis)</td>
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<td>• TM</td>
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<td></td>
<td>• QMS focal person(s)/lead(s)</td>
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<td></td>
<td>• Risk and opportunity responsibility matrix (based on responsible, accountable, consulted and informed (RACI principles)</td>
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<tr>
<td>8.</td>
<td>Develop and document SMART quality objectives including plan for M &amp; E with related required resources</td>
<td>6.6</td>
<td>Documented quality objectives (and their short and long term targets), resources, responsibilities (ideally in NRA’s strategic plan) and M &amp; E indicators</td>
</tr>
</tbody>
</table>
| 9. | Develop new or harmonize with existing procedures for control of measuring equipment, organizational knowledge management, personnel training and communication | 6.7 | Documented and implemented procedures for:  
- staff recruitment (based on defined competency framework for different levels and positions, training and re-training based on established gaps as per organisational competency framework)  
- management and maintenance of measuring equipment as applicable in making regulatory decisions (laboratory and/or inspection equipment)  
- management of organisational knowledge (e.g., retirements, resignations, and new knowledge acquisition)  
- management of internal and external communication of regulatory decisions, products, services and other engagements with customers and stakeholders  
- use of IT in technical and administrative processes including management of templates used in the software or equipment or in other procedures needed to manage resources as described in the guideline | TM  
QMS focal person(s)/lead(s) |
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<th>Description</th>
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<tr>
<td>10</td>
<td>Develop new or harmonize with existing procedures for all processes in technical and administrative units of NRA</td>
<td>6.8</td>
<td>Documented and implemented procedures for all applicable technical and administrative processes within NRA and that contain the appropriate level of detail based on the complexity of the processes and associated risks. The procedures should address all activities which are involved in provision of products and services as mandated by national legislations</td>
</tr>
</tbody>
</table>
| 11| Develop procedures for monitoring of customer satisfaction, internal audit, management review, and complaints handling, and put them in practice. | 6.9 | - Documented and implemented procedures for customer complaints and satisfaction along with publications of guidance to the public on the procedures and communication  
- Documented and implemented internal audit programs  
- Documented and implemented regular reviews of QMS implementation and performance by TM |
| 12| Develop procedures for corrections, corrective actions, and improvements, and put them in practice | 6.10 | Documented and implemented procedures for corrective actions and change management, along with a link for updating risk and opportunity management plans |
Abbreviations

NOTE: This section will be updated in the final stages of guideline development.

CREAM Clear, Relevant, Economic, Adequate and Monitorable
GBT Global Benchmarking Tool
HR Human Resources
ICT Information and Communication Technology
IT Information Technology
ISO International Standardisation Organization
KPI Key Performance Indicator
LI Licensing Establishments
LIMS Laboratory Information Management System
MA Marketing Authorization
M & E Monitoring and Evaluation
MC Market Surveillance and Control
MOH Ministry of Health
MS Member States
NRA National Regulatory Authority
PDCA Plan, Do, Check and Act
QA Quality Assurance
QMS Quality Management System
RACI Responsible, Accountable, Consulted and Informed
RCA Root Cause Analysis
SMART Specific, Measurable, Attainable, Realistic and Time-bound
SOP Standard Operating Procedure
SWOT Strengths, Weaknesses, Opportunities and Threats
TM Top Management
VL Vigilance (one of GBT regulatory functions)
WHA World Health Assembly
WHO World Health Organization
References


[18] WHO Guidelines on Quality Risk Management.

**References to the GBT VI**

The WHO GBT is used to assess the level of implementation of QMS in NRA. The QMS indicator consists of 14 sub-indicators that are used to identify the degree of QMS implementation and the existing gaps across the NRA.

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<th>Related GBT VI sub – indicators</th>
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PRODUCTION OF WATER FOR INJECTION
BY MEANS OTHER THAN DISTILLATION
(July 2019)

DRAFT FOR COMMENTS

Medicines Quality Assurance working documents will be sent out electronically and they will also be placed on the Medicines website for comments under “Current projects”.
http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.
PRODUCTION OF WATER FOR INJECTION
BY MEANS OTHER THAN DISTILLATION

BACKGROUND

In recent years, several pharmacopoeias adopted revised monographs on water for injection (WFI) allowing production by non-distillation technologies. Until now, the production of WFI in many countries was limited to distillation only. The monograph revisions in a number of pharmacopoeias were the result of extensive consultations with stakeholders and now allow production of WFI by a purification process equivalent to distillation – such as reverse osmosis – coupled with appropriate techniques. During the Fifty-second meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in October 2017, members of the Expert Committee recommended that the WHO Secretariat should collect feedback on whether or not to revise the WHO specifications and good manufacturing practices (GMP) in relation to the production of WFI. In light of this, feedback was sought on whether or not the WHO specifications and GMP text(s) should be revised in relation to the production of WFI, allowing other purification processes and, if yes, whether details on additional requirements should be added and, if so, which requirements these should be. A working document for public inquiry was circulated in March 2018 and comments received were consolidated in April 2018. The issue was discussed at an informal Consultation on Screening Technologies, Sampling and Specifications for Medicines held in May 2018 and then again during an informal Consultation on Good Practices for Health Products Manufacture and Inspection held in July 2018. Comments and feedback were then consolidated before presentation of the document and all comments to the Expert Committee in October 2018.

During the Fifty-third ECSPP meeting, the Expert Committee members discussed and agreed that the monograph in The International Pharmacopoeia, Water for Injections (1) and WHO Good Manufacturing Practices: Water for Pharmaceutical Use (2) be revised to allow different technologies for production of WFI other than distillation.

This specific text was drafted to clarify the use of alternative production of WFI.
1. **INTRODUCTION**

1.1. Water is widely used in the pharmaceutical industry. It is often used as a raw material, an ingredient in formulations, to prepare reagents, in cleaning and in the manufacture of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP).

1.2. Water for pharmaceutical use must meet quality requirements and specifications as published in standards and Pharmacopoeia. Water of required quality for its intended use should be produced by appropriate methods.

2. **SCOPE**

2.1. This document provides guidance for the production of WFI by means other than distillation. The principles described in this guideline may be applied to other grades of water produced, meeting other specifications.

2.2. The document is not exhaustive but aims to provide guidance on the main principles to be considered. Other guidelines and literature should also be consulted (1,2).

3. **MONOGRAPHS**

3.1. Manufacturers should have appropriate specifications for WFI.

3.2. Monographs for WFI are published in *The International Pharmacopoeia*, as well as various national Pharmacopoeia, and provide for the minimum requirements for the quality of WFI.

3.3. WFI should meet the specification as published in current monographs of the Pharmacopoeia, recognized by the Medicines Regulatory Authority.
4. **LIFE CYCLE APPROACH**

4.1. Good practices during each stage of the life cycle in the production and control of WFI should be considered.

4.2. Stages in the life cycle in production include, but are not limited to, the collection and treatment of source water, treatment of potable water and purified water used in production of WFI, production of WFI, storage, distribution, control and use of WFI.

4.3. Principles of risk management and data governance should be applied in each relevant stage of the life cycle.

5. **RISK ASSESSMENT**

5.1. An appropriate method for the production of WFI should be used.

5.2. Risks and controls should be identified for each stage of the life cycle of the production, storage, distribution, use and control of WFI.

5.3. Risks identified should be assessed to determine the scope and extent of validation and qualification of the system, including the computerized system, used for the production, control and monitoring of WFI.

5.4. Where production methods other than distillation are used, specific controls should be taken to ensure:

   - that there is no risk of contamination of water;
   - the appropriateness of user requirement specifications (URS);
   - feed-water quality;
   - sequence of purification stages required;
   - the extent of pre-treatment required;
   - appropriately designed and located sampling points;
   - controls are in place to prevent dead legs and contamination; and
   - in-line monitoring.
6. CONTROL STRATEGY

6.1. The WFI system should be appropriately qualified and validated.

6.2. There should be no risk of contamination of WFI produced, stored or circulated.

6.3. An appropriate control strategy should be defined to ensure that all risks identified are eliminated, or reduced to an acceptable level.

6.4. Attention should be given to, for example, the selection of components, their material of construction, preventive maintenance, life cycle and sanitization.

6.5. Treatment (also referred to as pre-treatment) of water entering the system should ensure adequate removal of chemicals (organic and inorganic), particles, matter and microbiological impurities. The treatment should not have a detrimental effect on materials of construction or downstream components of the water system.

6.6. Techniques such as deionisation, ultrafiltration, water softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a double pass reverse osmosis (RO) system.

6.7. The materials of construction of all parts of the system, including components selected for the production, storage and distribution of WFI systems, should be appropriately designed and constructed, should not be reactive, additive, absorptive or adversely affect the quality of water. Examples of suitable materials include SS 316L and a variety of polymers (e.g. Polyvinylidene Fluoride (PVDF) and Polypropylene (PP)).

6.8. These should allow for routine sanitisation (thermal or chemical, or a combination thereof). The method of sanitisation should be appropriate, effective and validated. Sanitization should be done at specified intervals in accordance with a documented procedure.

6.9. Appropriate sampling techniques should be used to sample water for analysis, at defined sampling locations, in accordance with a documented sampling procedure and a schedule.
7. **GOOD PRACTICES IN THE PRODUCTION OF WFI**

7.1 WFI should be prepared either from water that complies with WHO guidelines for drinking-water, national standards for drinking water or purified water as a minimum quality feedwater.

7.2 An appropriate method should be used to produce WFI.

7.3 Where RO is used, single or double-pass RO, coupled with other appropriate techniques such as electro-deionisation (EDI), ultrafiltration (UF) or nanofiltration, should be considered. The purification process employed should be proven to be at least equivalent to distillation.

7.4 WFI should meet the relevant pharmacopoeia specifications for chemical and microbiological purity (including endotoxin).

7.5 Water testing results should be trended. Trend data should be reviewed routinely in order to determine the potential for deterioration in the system.

7.6 Appropriate action and alert limits in addition to specification limits should be specified. Alert and action limits should be reassessed routinely to enable, where possible, a re-evaluation of those control limits.

7.8 The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, pH, total organic carbon (TOC) and microbial contamination.

7.9 A combination of online and offline monitoring of WFI should be done to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with on-line instruments.

7.10 RO membranes should be monitored for any potential integrity breaches.

7.11 The system should remain in a validated state throughout its life cycle.
References


Further reading

ISPE Baseline. Water and Steam Systems. Volume 4

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POLICY ON REMAINING SHELF-LIFE OF MEDICAL PRODUCTS UPON DELIVERY*

(July 2019)

DRAFT FOR COMMENTS

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http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.

*Explanatory note : « delivery » could mean delivery at different stages of the supply chain
POLICY ON REMAINING SHELF-LIFE
OF MEDICAL PRODUCTS UPON DELIVERY

1. INTRODUCTION

Following discussions relating to establishing policy for remaining shelf-life (RSL) of medical products upon delivery, and considering the discussion between the Interagency Pharmaceutical Coordination (IPC) group representatives, it was decided to initiate a project to establish a policy on remaining shelf-life for procurement and supply of medical products.

The concept and project to establish such a policy was also discussed during the meeting of the Fifty-third Expert Committee on Specifications for Pharmaceutical Products (ECSPP) in October 2018. It was noted that some guidance documents were available from different procurement agencies. It was agreed that the World Health Organization (WHO) would initiate the discussion and preparation of a policy whilst following the WHO process for the establishment of such a policy paper.

Information and policy on remaining shelf-life was collected from different agencies and interested parties and a first draft document was prepared after an informal discussion meeting in Geneva, Switzerland, in January 2019.

It was then agreed that the policy should not cover only finished pharmaceutical products but should be extended to also cover other products including, but not limited to, medical devices, vaccines and in vitro diagnostics (IVDs). (These products are collectively referred to as “medical products” hereafter).

A draft document was prepared and circulated to IPC members, as well as other interested parties, inviting comments. The comments received were reviewed during an informal discussion meeting in June 2019 and the draft document was updated.
The aims of this policy document are:

- to ensure that there is a balance between enforcing the remaining shelf-life policy and ensuring availability of medical products;
- to facilitate the national authorization of importation of medical products where applicable;
- to promote and support the efficient processing of medical products in the supply chain at all levels and thus prevent wastage because of delays;
- to assist in ensuring that there is sufficient stock of medical products, with acceptable remaining shelf-life, in-country;
- to prevent dumping of medical products;
- to ensure that barriers to access and supply of medical products are addressed;
- to prevent stock-outs;
- to prevent receiving donations of medical products that are not in accordance with this guideline; and
- to prevent having expired stock of medical products.

The policy contained in this document is intended to provide guidance on remaining shelf-life of medical products upon delivery and should be implemented by all stakeholders in the supply chain of medical products. It is also recommended that the policy be considered in the national policy of countries.

2. **SCOPE**

The principles contained in this document should be applied to medical products in the supply chain. This includes donated products. *(See WHO Guidelines on Donations).*

This document presents policy on shelf-life and does not address details contained in other guidelines, guides and agreements between different parties in the supply chain.

As “kits” are made up of different products, and due to certain specifics related to the shelf-life of kits, these are not included in the scope of this guideline. The principles contained in this guideline may however be used in considering the remaining shelf-life of kits.

All stakeholders, including manufacturers, suppliers, donors and recipients should implement the shelf-life policy contained in this document.
3. GLOSSARY

(Note: the definitions below are taken from existing WHO guidelines where available, or alternatively, from other recognised guidelines).

**Batch**
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

**Consignment (or delivery)**
The quantity of a pharmaceutical or pharmaceuticals, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

**Expiry date (or expiration date)**
The date placed on the container or labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.

**Finished pharmaceutical product (FPP)**
A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

**Install by date**
The date by which an instrument, device or other has to be installed.

**Manufacture**
All operations of purchase of materials and products, production, quality control (QC), release, storage and distribution of pharmaceutical products, and the related controls.

**Manufacturer**
A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.
Marketing authorization (product licence, registration certificate)
A legal document issued by the competent medicines regulatory authority that establishes the
detailed composition and formulation of the product and the pharmacopoeial or other recognized
specifications of its ingredients and of the final product itself, and includes details of packaging,
labelling and shelf-life.

Manufacturer (IVD)
Means any natural or legal person with responsibility for design and/or manufacture of an IVD
with the intention of making the IVD available for use, under his or her name, whether or not
such an IVD is designed and/or manufactured by that person him- or herself or on his or her
behalf by (an)other person(s)

Manufacturing date
The date of production of a batch is defined as the date that the first step is performed
involving the combining of the active ingredient with other ingredients. Where there are no
other ingredients than an Active ingredient, the date of the start of the processing or filling
operation is considered as the date of production. (Adapted from EU.)

Medical product
Products including, but not limited to, finished pharmaceutical products, medical devices,
vaccines and in vitro diagnostics (IVDs).

Pharmaceutical product
Any material or product intended for human or veterinary use presented in its finished dosage
form, or as a starting material for use in such a dosage form, that is subject to control by
pharmaceutical legislation in the exporting state and/or the importing state.

Production
All operations involved in the preparation of a pharmaceutical product, from receipt of materials,
through processing, packaging and repackaging, labelling and relabelling, to completion of the
finished product.

Remaining shelf-life
Defined as the period remaining, from the date upon delivery, to the expiry date, retest date,
install by date or other use before date established by the supplier
Retest date
The date when a material should be re-examined to ensure that it is still suitable for use.

Shelf-life
Shelf-life is the period of time, from the date of manufacture, that a product is expected to remain within its approved product specification while handled and stored under defined conditions.

Upon delivery
Means the date the medical product is delivered as specified, e.g. at the port; at the point in country after customs clearance, or at the end-user – and as defined in the agreement between relevant parties.

4. THE NEED FOR POLICY

As there was no harmonized policy on remaining shelf-life for medical products amongst procurers, donors and recipient countries, it was agreed that it will be beneficial to have a harmonized approach on policy for remaining shelf-life. This will assist national regulatory authorities (NRAs), suppliers, donors, procurers, importers and distributors to manage medical products throughout the supply chain, thus ensuring the availability of quality medical products within the remaining shelf-life reaching the end-user. The authorization of importation of medical products by NRAs sometimes delays access to medical products. A harmonized approach among countries may facilitate authorization and release of medical products in the supply chain in a timely manner.

This policy document is not a standalone document. It should be read with other documents, guides and guidelines including, but not limited to, WHO guidelines such as Stability Testing, Good Storage and Distribution Practices, Donations, Model Quality Assurance System for Procurement Agencies (MQAS), Pharmacopoeia and International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.
5. POLICY ON REMAINING SHELF-LIFE

Note: The manufacturing date of a medical product should be defined by the manufacturer and be provided upon request, e.g. when this is not on the packaging.

Principles

Policy on remaining shelf-life should be realistic. It should be defined for medical products and be based on factors such as, but not limited to, the category and type of product, inventory level, storage condition and resources in-country.

There should be agreements between suppliers, purchasers and recipients covering the relevant responsibilities of each party, including remaining shelf-life.

Products should be transported, received, stored and distributed in accordance with WHO Good Storage and Distribution Practices (GSDP). Special attention should be given to temperature, light and moisture sensitive products.

Products supplied by the manufacturer or supplier should meet the policy of national government and the recommendations in terms of remaining shelf-life prescribed in this guideline. Compliance with this requirement may be verified by an appropriate means, such as a pre-shipment inspection or other.

Products should be appropriately labelled. The label should include the expiry, re-test or install by date, as appropriate. Products with an “Install by” date should be installed prior to the date specified by the supplier.

Products received should be scrutinised in an attempt to identify possible substandard and falsified products. It should be ensured that, for example, the expiry date is not falsified. (See Guidelines on Substandard and Falsified Products, WHO Guidance on Testing of “suspect” falsified medicines.)

Where different periods for remaining shelf-life have been defined for products, recipients should ensure that the products meet the remaining shelf-life requirement for the intended destination, e.g. central warehouse, regional warehouse, testing site or user point.
National authorization for importation, where required, should be obtained based on the available information, including the shelf-life or expiry date of the product as well as the remaining shelf-life (where possible), to assist in expediting approval.

Where so justified, suppliers, recipients and national authorities may negotiate deviations from the remaining shelf-life policy provided that:

(a) the medical product quality will be assured;
(b) where the shelf-life is shorter than stipulated in the policy, it is ensured that the stock will be consumed prior to expiry;
(c) the medical product should reach end-users with adequate remaining shelf-life to show confidence on the quality of the medical product and time to consume it before expiry.

Risk assessment to ensure that the parameters are met should be done, taking into account at least the following criteria:

- type of product: different criticality for the safety of the patient between pharmaceutical products, vaccines, medical devices and IVDs;
- existing shelf-life: with this the remaining shelf-life at delivery time can be estimated;
- compliance with WHO GSDP guidelines;
- order frequency (based on consumption): recipients and end-user should regularly verify that medical products in stock are rotated or used within their remaining shelf-life and adjust the quantities ordered to make sure that the medical products will be used during their remaining shelf-life;
- assessment of the real needs, to ensure that the medical products can be used within their shelf-life;
- emergency: during an emergency situation, the remaining shelf-life policy should be well balanced to ensure that patients will receive the medical products in time;
- the logistic set-up: the premises location, number of transportation means and its agility will have an impact on the speed of the delivery and, hence, have the products being used before their expiry date;
- the activity specificities: similarly, whether the medical products will be used by the national programme, or at own driven activities managed directly by the importer, will make a difference in terms of speed of delivery to the end-user;
- the point of delivery: national warehouses, importer or end-user facilities will also have an impact on the speed of delivery.
Expiry date

Products, such as pharmaceutical products, should have an expiry date allocated by the manufacturer. The expiry date should be established based on stability testing results obtained in the relevant packaging (primary, and secondary packaging, where appropriate) and required stability conditions. (See WHO Guideline: Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. WHO Technical Report Series, No. 1010, Annex 10, 2018.)

Retesting

Where a manufacturer or supplier has obtained approval from an NRA for a new or extended shelf-life, this may be applied.

Products with an expiry date should not be subjected to retesting by the purchaser or recipient for the purpose of extension of shelf-life. Only in exceptional cases, such as product shortages, should a recipient consider to extend the expiry date of received batches subject to certain conditions, such as availability of scientific data, the application of risk management principles and NRA approval. The new expiry date should be reflected on the packaging.

Products with a retest date allocated by a manufacturer or supplier should have at least one year of shelf-life remaining (from the date of delivery to the enduser, to the labelled retest date). Products with a retest date allocated by a manufacturer, e.g. chemicals and reagents, may be retested and used if the quality parameters are met.

Examples of considerations and recommended remaining shelf-life of products are given in the Annexure.
References

[Note from the Secretariat: The references will be completed in the final text.]

Further Reading

   Short name: WHO TRS No. 986, Annex 2

   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

   Short name: WHO TRS No. 961, 957), Annex 1

   Short name: WHO TRS No. 961, Annex 9
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

8. WHO Guidance on Procurement of IVDs and Related Laboratory Items.  
https://apps.who.int/iris/bitstream/handle/10665/255577/9789241512558-eng.pdf?sequence=1

https://apps.who.int/iris/bitstream/handle/10665/259742/WHO-BS-2017.2304-eng.pdf?ua=1

10. Annex to TGS-2 Establishing Component Stability for In Vitro Diagnostic Medical Devices.  
https://apps.who.int/iris/bitstream/handle/10665/311345/WHO-MVP-EMP-RHT-PQT-2019.03-eng.pdf?ua=1


WHO/UNITED NATIONS POPULATION FUND (UNFPA) PREQUALIFICATION PROGRAMME GUIDANCE FOR CONTRACEPTIVE DEVICES: MALE LATEX CONDOMS, FEMALE CONDOMS AND INTRA-UTERINE DEVICES

(July 2019)

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WHO/UNITED NATIONS POPULATION FUND (UNFPA) PREQUALIFICATION PROGRAMME GUIDANCE FOR CONTRACEPTIVE DEVICES: MALE LATEX CONDOMS, FEMALE CONDOMS AND INTRA-UTERINE DEVICES

BACKGROUND

Extract from the Fifty-third World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) meeting report:

“Ms Seloi Mogatle and Dr William Potter from the United Nations Population Fund (UNFPA) gave an update on the prequalification guidance for contraceptive devices and condoms at the Fifty-third Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) that took place at the World Health Organization (WHO) headquarters in Geneva, Switzerland, October 2018. The UNFPA had contacted WHO to inquire how best to start a process to update the process of the following texts that were adopted by the ECSPP and published in 2008. The Expert Committee agreed to the importance of updating these materials in view of the changes in the contraceptive field globally over the previous decade. The two organizations committed to work together to bring the documents up-to-date. It was suggested by UNFPA to separate out the current existing procedure for condoms to include the following aspects:

5. Condom Quality Assurance and Annexes.
7. Condom Storage and Transportation.
UNFPA also raised the issue of specifications for lubricants (both water-based and silicon-bases) which needs to be considered when developing the new guidelines. The Expert Committee supported the development of the relevant documents in consultation with the WHO Secretariat, the preparation of these for public consultation and took note that they will be reported back to the Expert Committee.”

The following documents are undergoing a public consultation as part of this series:


6. QAS/19.806 - WHO/UNFPA Specifications for Plain Lubricants.

INTRODUCTION

The United Nations, through its procurement agencies, supplies medicines and other health products to countries throughout the world in order to improve access to a choice of products of acceptable quality, safety and efficacy.

WHO, UNFPA and other key partners developed an evidence-based list of Reproductive Health Essential Medicines (2005) which was subsequently approved by the WHO Expert Committee on Selection and Use of Essential Medicines. From this list, and the recommendations of members of the Reproductive Health Supplies Coalition, it was agreed that WHO would include a core group of contraceptive essential medicines in the Prequalification Programme, the implementation of which began in 2006. As part of this activity, it was agreed that UNFPA would take responsibility for the prequalification of copper-bearing intrauterine devices (IUDs) and male latex condoms, and that the UNFPA scheme would be harmonized with that of the WHO Prequalification Programme.

This document describes the implementation of the WHO UNFPA Prequalification Programme for contraceptive devices (male latex condoms, female condoms and intra-uterine devices).

The Prequalification Programme was approved in principle and subject to confirmation following an external review for publication by the Forty-second ECSPP in October 2007.

The Prequalification Programme is supported by a specific UNFPA management system with detailed standard operating procedures (SOPs).

The WHO/UNFPA Prequalification Programme involves the following key activities:

- the evaluation of documents submitted in response to an invitation for Expression of Interest (EOI);
- the inspection of each manufacturing site per product;
- product testing;
- the review of testing and inspection reports to make a decision about the acceptability of each product and its specific manufacturing site; and
- the periodic reassessment of the prequalification status of products and manufacturing sites.

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1.1 Objectives

The overall objective is to implement a scheme to prequalify manufacturers of contraceptive devices of assured quality, at specific manufacturing sites, for procurement by United Nations agencies and other bulk procurement agencies. Specific objectives are to:

- promote the procurement of contraceptive devices from manufacturing sites that have been ascertained to have the capacity to produce good-quality products;
- establish a system that promotes the procurement of good-quality products that retain their effectiveness throughout their stated shelf-life and conform to the latest edition of the international standard\textsuperscript{3} for the product;
- broaden the base of suppliers for contraceptive devices that are deemed acceptable, in principle, for procurement by United Nations agencies and other bulk procurement agencies; and
- maintain and publish the list of prequalified suppliers.

2. THE PREQUALIFICATION PROGRAMME FOR REPRODUCTIVE HEALTH DEVICES

2.1 Eligibility to participate

The Prequalification Programme is intended for manufacturers who carry out all key manufacturing steps as specified by UNFPA in the call for an EOI referred to in clause 2.2, below.

For male latex condoms, this entails manufacturers who undertake the processes of formulation, compounding and dipping, lubrication, testing, as well as for manufacturers using pre-vulcanized latex.

For female condoms, this entails manufacturers who undertake the processes of formulation, compounding and dipping, lubrication, testing, and who undertake at least the formation of the sheath, testing and packing.

For intra-uterine devices, this entails manufacturers that undertake the process of moulding, assembly, packaging and control of sterilization. One or more of these processes may be carried out on a contract basis but the manufacturer retains overall responsibility for product quality.

\textsuperscript{3} Refer to Annex II: for full list of relevant standards
The Prequalification Programme does not apply to agents, distributors or suppliers engaged only in testing, lubricating and primary packaging.

2.2 Application for Prequalification: Expression of Interest

2.2.1 Calls for and submission of Expressions of Interest

Invitations to interested parties to submit EOI are published at regular intervals on the web sites of UNFPA (http://www.unfpa.org/public/procurement).

The invitation is open and transparent and invites manufacturers and/or their agents, as described in clause 2.1 above, to submit EOIs for the products listed in the invitation. The manufacturers should submit their EOIs to the UNFPA focal point with the relevant information requested in the invitation. Manufacturers that are applying for a requalification/assessment should submit the EOI the year before the re-inspection is to take place (see clause 2.9, Reassessment). If a manufacturer has more than one site, each site must submit a separate application. The manufacturers will be given a specified period to submit their responses from the time of publication of the advertisement. The information must be submitted in English (see clause 2.10, Language).

UNFPA will receive and record the EOI from each manufacturer and issue an acknowledgement of receipt.

WHO and UNFPA will provide further guidance on the submission of documentation for prequalification and make such guidance available on the UNFPA and WHO web sites.

When submitting an EOI, the manufacturer should send to the UNFPA focal point the following:

- a covering letter expressing interest in participating in the WHO/UNFPA Prequalification Programme and confirming that the information submitted in the Summary Technical Documentation (STED) is complete and correct; refer to Annex I for a sample cover letter.
- a STED as specified in the WHO/UNFPA technical specification for male latex condom, female condoms or intra-uterine devices for submitting product data and information; and
- ten product samples in its primary package, as examples of products produced; for each type mentioned in the STED (if applicable).
The STED must be accompanied by copies of all current certifications/accreditations; all manufacturing licences/registrations held; a copy of the company registration; copies of certificates and relevant documentation as applicable in the country of manufacture; documentation of the principal place of incorporation (for those that are corporations); specific certification/licences required in the country for manufacturing and exporting; and other legal documents, such as trading certificates.

The documentation must be submitted in English, as described in Section 2.11 below. Documents not in English must be submitted with certified translations. The manufacturer must provide an electronic version (CD or USB key to be sent by courier or registered mail or email) of this material.

### 2.2.2 Assessment of documents submitted

The aim of the assessment of the submitted documentation is to determine whether the manufacturer is certified to ISO 13485 and other appropriate ISO standards, and has appropriate regulatory approvals, manufacturing capacity, factory documentation and legal status, and in principle is capable of meeting the *WHO/UNFPA Specification* with respect to product quality and safety to warrant inspection by UNFPA.

#### 2.2.2.1 Initial screening of documentation

UNFPA will aim to screen the documentation within 30 days of the closing date for receipt of responses to ascertain whether or not it contains all the required information.

If the submission is incomplete, the manufacturer will be informed and requested to complete the STED within a specified time period. If the dossier remains incomplete, it may be rejected.

STEDs that are considered complete following the administrative screening will be retained by UNFPA for evaluation.

UNFPA will exchange letters with the manufacturer covering provisions of confidentiality and the process of assessment of submitted information and the scheduling and procedure of the site inspection.
2.2.2.2 Assessment of the Summary Technical Documentation

UNFPA will appoint suitably qualified and experienced experts to complete the assessment of the STED within 90 days of the closing date for receipt of responses.

The assessment of the submitted documentation will be done in accordance with SOPs established by UNFPA for that purpose. To ensure uniformity in evaluation and timeliness of assessment activities, UNFPA will, if needed, provide training to the assessors on the procedures that are specific to UNFPA.

In making its assessment, UNFPA may take into account information submitted by the manufacturer during previous applications that may be in UNFPA’s possession, including results from previous site inspections and laboratory test results on the relevant products produced by the manufacturer.

UNFPA aims to advise the manufacturers of the outcome of the assessment of the documentation within 30 days after its completion. If applications are found to be in compliance with the requirements of UNFPA, as detailed in the operational guidance for the product, and on the WHO and UNFPA web sites, the manufacturing site will be scheduled for inspection.

2.2.2.3 Technical experts hired by UNFPA

Profile

Document assessments and inspections are carried out by technical experts appointed by UNFPA. The technical experts are selected through an international competitive bidding process to select individuals that have documented qualifications, detailed knowledge of the process for manufacturing contraceptive devices, experience in auditing and quality management systems, and specific experience inspecting manufacturing sites of contraceptive devices.

The document assessment and inspection may include one or more experts. The assessor may be responsible for subsequent inspections of the manufacturing site, depending on the contraceptive device. The experts must comply with the confidentiality and conflict of interest rules of UNFPA as laid down in clauses 3 and 4 of this guidance document.
2.3 Site inspection

UNFPA will plan and coordinate inspections at the manufacturing sites to assess:

- the manufacturing facilities
- the manufacturing process
- the quality management systems
- product quality

for compliance with the requirements of the *WHO/UNFPA Specification* and good management practice, including the international standards relevant to the product as in Annex II.

### 2.3.1 Inspection team

The inspection will be performed by a team of inspectors consisting of experts appointed by UNFPA, who will conduct the assessment on behalf of UNFPA. The inspectors must have documented qualifications, detailed knowledge of manufacturing processes, expertise in auditing and quality management systems, and specific experience in inspecting condom and IUD manufacturing sites. The inspectors must comply with the confidentiality and conflict of interest rules of UNFPA, as detailed in clauses 3 and 4 of this guidance document. To ensure uniformity in inspection procedures, UNFPA has prepared an SOP and, if necessary, can provide training to these experts.

Where possible, UNFPA will appoint at least one inspector able to communicate in and read the local language. Failing this, an interpreter selected by UNFPA will be used. One member of the team will be designated by UNFPA as the “lead inspector” and will be responsible for directing the on-site inspection activities and the production of the report. The team may include observers from UNFPA. UNFPA will advise and seek the involvement of the national competent body in the on-site inspection.

UNFPA will advise the manufacturer in advance of the composition of the team performing the site inspection and the identity of each inspector. The manufacturer has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member’s participation in the site visit. Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of information on the composition of the proposed team. UNFPA will consider the objection and, if it is upheld, a replacement inspector will be appointed.
So as to ensure a standardized approach, each team will perform the inspections and report on its findings to UNFPA in accordance with the SOPs established by UNFPA for that purpose.

Information submitted in response to the invitation for EOI and the assessment report will be made available to the inspectors. All inspectors must comply with the confidentiality and conflict of interest rules of UNFPA as detailed in clauses 3 and 4.

2.3.2 Scope and scheduling

Prior to the inspection, the manufacturer will be informed of the scope of the inspectors’ planned activities. The key components of the inspection are described in the operational guidance of the relevant technical specification of the product and on the WHO and UNFPA web sites. The inspection may not be limited to these components. Manufacturers must be prepared to show the inspectors all aspects of the facility, including records and data that relate to the production of the condoms. UNFPA aims to advise the manufacturer of the date of inspection at least 30 days in advance. UNFPA and the inspectors will make efforts to accommodate reasonable requests by the manufacturers and national regulatory authorities to change the date of inspection.

UNFPA will inform the manufacturer that the inspectors may request copies of specific documents for review during inspection and may request permission to take photographs during the inspection, subject always to considerations of confidential information as referred to in clause 3 of this document.

2.3.3 Transparency

The inspection team is paid by UNFPA to inspect the facilities and the members are reimbursed for their hotel and transport expenses by UNFPA. The manufacturer will not pay for hotel accommodation or make any payments for or to the inspectors and/or UNFPA staff. The manufacturer may be requested to assist in making reservations at an appropriate hotel and arrangements for local transportation between the hotel and manufacturing facilities.

The inspectors (and UNFPA staff who accompany the inspectors) cannot accept any gifts from the companies they visit. UNFPA requires that manufacturers do not make any offers of gifts of whatever value to the inspectors and/or UNFPA staff.
By participating in the Prequalification Programme, the manufacturer agrees to allow full access to:

- any of the facilities that are in any way involved in the production, packaging and storage of the product(s) concerned; and
- all documentation related to that production.

If such access is not provided, the inspection will not be completed, and the manufacturing site and specific products cannot be prequalified. Any evidence of fraud or serious omissions by the manufacturer in the initial assessment procedure or the inspection will lead to termination of the site inspection.

2.4 Product testing

Products will be sampled for independent testing according to the sampling requirements for prequalification testing specified in the Technical Specification: WHO/UNFPA Male Latex Condom Specification or the WHO/UNFPA Female Condom Generic Specific Specification or the Tcu380A Technical Specification.

Products will be sampled for independent testing prior or subsequent to the inspection under the supervision of, or by, an independent sampler appointed by UNFPA or by the inspectors at an appropriate point during the site inspection. As a component of their prequalification application, manufacturers shall submit a copy of their production plan for the coming year to enable UNFPA to communicate the number of samples from each production Lot the manufacturers should retain for prequalification testing and/or to schedule the inspection during a time when ample Lots will be available for sampling. Sampling and testing will be conducted in accordance with the requirements detailed in the WHO/UNFPA TCu380A IUD Technical Specification. All product testing will be undertaken by independent test laboratories selected by UNFPA, of defined and documented competence and experience, as demonstrated by accreditation to the current ISO 17025 standard with testing of IUDs within the scope of its accreditation. The sample will be packed and sealed by the inspector or the independent sampler as appropriate. The inspectors may take the sample with them or arrange for the manufacturer to have the sealed box sent to the selected laboratory by courier at UNFPA’s expense.

The manufacturer will be provided with a copy of this test report.
2.5 Reporting and decision to prequalify

At the conclusion of the inspection, the inspectors will prepare a brief written summary report outlining the key findings and observations discussed with the manufacturer during the site inspection. This report will be provided to UNFPA with a copy to the manufacturer.

Manufacturers should not submit corrective actions to UNFPA in response to this summary report but only in response to the official inspection report that is issued. The official inspection report prepared by the inspection team will be issued by UNFPA to the manufacturer four to six weeks following the inspection.

The report will indicate one of the following recommendations:

- requalify the product manufactured at a specific site without conditions. This will only be the case when there is no evidence that corrective action is required.
- Require the manufacturer, where deemed necessary, to undertake specified corrective and preventive action(s) (CAPA).
- Determine that product and manufacturing site is ineligible for prequalification (without any requirement for corrective action being offered). This will not, however, preclude the manufacturer from resubmitting an application in response to future invitations for EOIs.

If any additional information is required, or corrective action has to be taken by the manufacturer(s), UNFPA will postpone its decision on the acceptability of the site(s) involved until such information has been evaluated or the corrective action has been taken and found satisfactory in accordance with the time frame and recommendations made by the inspectors.

The inspection report may contain non-conformities and observations. The findings of the inspection may include non-mandatory observations aimed at highlighting potential for improved manufacturing and quality management practices. Non-conformities are classified as major or minor. A manufacturer that receives a major non-conformity cannot be prequalified and, if already prequalified, status may be suspended. A major non-conformity will require submission of corrective and preventative actions and a possible re-inspection. Minor non-conformities require corrective and preventative action to be submitted to UNFPA by the manufacturer in the stated period in order to achieve or maintain prequalification. Observations made by the inspectors are intended to highlight opportunities to improve quality management practices. It is strongly recommended that manufacturers consider acting upon any observations made, but prequalification is not dependent upon this.
Where the UNFPA recommends corrective action, the manufacturer must advise UNFPA within an agreed period of time that corrective action has been completed and provide the relevant evidence, if required. The recommendation for corrective action may include further independent product testing or re-inspection. After review of the evidence, UNFPA will decide whether or not to schedule a further inspection.

Corrective and preventive action (CAPAs) submissions should be submitted to UNFPA electronically in response to the official inspection report. Evidence of action shall be provided. Evidence of actions taken should be supplied to UNFPA in the form of SOPs, pictures or other appropriate formats. The files submitted shall be organized and clearly labelled. Each manufacturer will normally be permitted two rounds of CAPA reviews. The first submission of corrective and preventive actions shall be in possession of UNFPA within 90 days of receipt of the official inspection report unless otherwise agreed with UNFPA. If a manufacturer has not successfully addressed all non-conformities raised during the inspection following the second CAPA review, the manufacturer may be asked to submit a fresh EOI for prequalification. The EOI should only be submitted when the manufacturer demonstrates compliance with the Prequalification Programme requirements. Any exceptions to this will be evaluated on a case-by-case basis.

If a further inspection is deemed necessary, the inspection process and assessment will be implemented in accordance with the procedure detailed in clauses 2.3, 2.4, 2.5 and 2.6 of this document. Any re-inspection may be at the expense of the manufacturer.

If evidence supporting mandatory improvement actions or additional information is required, or other corrective actions have to be taken by the manufacturer, UNFPA will postpone its final decision until such information has been evaluated or the corrective action has been taken and found satisfactory.

If the manufacturer has not submitted a satisfactory response within 12 months of submission of the report from UNFPA, the application will lapse and the manufacturer will need to reapply in response to a future invitation for an EOI.

Each manufacturer will receive a letter from UNFPA informing it of the outcome of the quality assessment process. UNFPA aims to inform the manufacturer formally of the results of the process within 30 days of receipt of all final reports.
UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the manufacturer is:

- not able to provide the required information; and/or
- unable to implement the corrective actions in a specified time period; and/or
- if the information supplied is inadequate to complete the quality assessment process.

Each manufacturer will receive a letter from UNFPA informing the manufacturer of the outcome of the quality assessment process. UNFPA aims to inform the manufacturer of the results of the process within 30 days of receipt of all final reports. Manufacturers will verify the final report that is produced for accuracy. In the event of any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA detailing the handling of appeals and complaints will be followed to discuss and resolve the issue. The ownership of any of the reports produced during the course of, or as the result of the assessment of documentation, product testing and inspection of the manufacturing site, lies with UNFPA. Thus, UNFPA shall be entitled to use and publish such reports and/or a summary of a report, subject always, however, to the protection of any commercially confidential information of the manufacturer(s).

Confidential information may include:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trademarks and/or patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the STED or inspection of the manufacturing site(s), between UNFPA and each manufacturer.

Notwithstanding the foregoing, UNFPA and WHO may share a summary and/or the full evaluation and inspection reports with the relevant authorities of any interested Member State of UNFPA and/or WHO. Confidential information submitted by the manufacturer that is marked “confidential” will not be included in the full evaluation and inspection reports without the permission of the manufacturer.
2.6 Listing of prequalified contraceptive devices and manufacturing sites

Once UNFPA is satisfied that the quality assessment process is complete and where the STED and corresponding manufacturing site have been found to meet the prequalification requirements, the product produced at the specified manufacturing site(s) will be listed on the WHO and UNFPA prequalification web sites.

The list of prequalified contraceptive devices and corresponding manufacturing sites will be compiled and updated in accordance with an SOP established by UNFPA for this purpose.

2.7 Maintenance of prequalification status

Once the product and the corresponding manufacturing sites are included in the list of prequalified manufacturers, the manufacturer is required to advise UNFPA, within four weeks, of any matter that affects the information on which the approval was based. This includes but is not limited to:

- change of premises;
- change in production and testing equipment;
- change in senior management;
- product recalls;
- change in certifications or licences held by the manufacturer;
- reports of adverse events;
- change in device design;
- change in suppliers key raw materials and components not previously listed in the STED;
- change in specification of raw materials, components and primary packaging materials;
- change in packaging;
- change in formulation;
- change in process and/or technology;
- change in production capacity; and
- new information about shelf-life.

It is the manufacturer’s responsibility to provide UNFPA with the appropriate documentation (referring to relevant parts of the STED) to prove that the implementation of any intended variation will not have an adverse impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs and communicate the outcome to manufacturer. Compliance with the requirement to report changes will be checked during the requalification inspection and processes carried out by UNFPA.
2.8 **Periodic monitoring of the quality of products produced by prequalified manufacturing sites**

At periodic intervals, UNFPA may, through an independent sampler, take random samples of contraceptive devices produced by listed manufacturers. Samples will be taken from intact lots stored in the manufacturer’s or distributor’s warehouse. The sample size will be in accordance with the current international standard for the contraceptive devices. The range of tests to be conducted will be in accordance with lot-by-lot pre-shipment compliance testing as detailed in the WHO/UNFPA Technical Specification of the product.

All product testing will be undertaken by an independent test laboratory, selected by UNFPA, of defined and documented accreditation to the current *ISO 17025* international standard. In the event of failure to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer and/or, if different from the manufacturer. UNFPA may request reports from consumer or regulatory authorities or from other procurement agencies relating to the quality and supply of the prequalified contraceptive device.

Complaints communicated to UNFPA concerning contraceptive devices procured through this Prequalification Programme will be investigated in accordance with an SOP established by UNFPA for that purpose. After investigation, UNFPA will provide a written report of the complaint investigations, including recommendations for action, to the manufacturer. UNFPA will require evidence of effective action taken, where relevant.

UNFPA will make the report available to the appropriate authorities of the country where the manufacturing site is located when necessary in the interest of public health, subject always to consideration of commercially confidential information, as referred to earlier in this document. UNFPA reserves the right to make such reports public, if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or recommendations for action with WHO and relevant authorities of interested Member States of the WHO. At periodic intervals, UNFPA may request a summary of the statistical analysis of product production from the manufacturer for demonstration of continued capability to manufacture to the WHO/UNFPA Technical Specification. This may be accompanied by a request for selected evidence from management review, risk management, production, measurement and analysis and other records.
2.9 Reassessment of prequalified manufacturing sites – requalification

UNFPA aims to undertake a reassessment of products manufactured at a specific site at intervals of three years and no more than five years. Such reassessments will consist of a comprehensive evaluation of documentation, site inspection and product testing similar to the initial prequalification assessment, as determined by a risk based assessment. Prequalified manufacturers should submit an EOI (application) for reassessment the year before they are due for a requalification inspection.

Reassessment may also be required in the following situations:

- if the contraceptive devices supplied by the manufacturer are considered by UNFPA or by one or more of the other United Nations agencies not to be in compliance with the agreed *WHO/UNFPA Specification* and pre-shipment compliance testing requirements;
- if a complaint considered serious in nature has been received by UNFPA or one or more of the other United Nations agencies or organizations; and
- if there is a significant change in the manufacturing process in respect to one or more of the items listed in clause 2.7, above.

All relevant information, including the reassessment of submitted documentation and site inspection reports, together with monitoring information, will be considered by the designated UNFPA official, and a decision will be made to either:

- maintain the contraceptive device and its manufacturing site on the list of prequalified products without need for corrective actions; or
- maintain the prequalification status of the contraceptive device and its manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, further product testing and/or a site inspection; or
- suspend the prequalified status.

UNFPA aims to advise the manufacturer of the result of the reassessment and make any necessary amendments to the list of prequalified manufacturing sites and products within 30 days of receipt of the data on the basis of which the decision is made. The updated list will be published on the WHO and UNFPA prequalification web sites.

UNFPA will de-list any prequalified product and manufacturing site if the submitted information is subsequently found to be incorrect or fraudulent. UNFPA will issue a notice of listing and delisting and inform appropriate authorities.
2.10 Language

The official language of the programme is English. All documents submitted as part of an application for prequalification will be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original plus a certified translation into English. All correspondence between UNFPA and the manufacturer should be in English. All reports issued by the assessors, inspectors and UNFPA on the assessment and inspections will be in English.

Inspections will be conducted in English, where necessary with the aid of an interpreter. It is the responsibility of the manufacturer to advise UNFPA and for UNFPA to agree whether or not an interpreter is required for the inspection.

2.11 Fees

At present, UNFPA will cover the expenses of the assessments, inspections and product testing. Manufacturers are responsible for their own costs related to providing the necessary information and help required under the Prequalification Programme.

Currently, the prequalification and re-qualification process is conducted by UNFPA free of charge. Subject to future decisions, UNFPA reserves the right, to charge a fee on a cost-reimbursement basis.

2.12 Resolution of disputes

If there is any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.
3. CONFIDENTIALITY UNDERTAKING

The assessors and inspectors will treat all information to which they gain access during the evaluations and inspections or otherwise, in connection with the discharge of their responsibilities in regard to the above mentioned project, as confidential and proprietary to UNFPA and parties collaborating with UNFPA in accordance with the terms set out below.

Assessors and inspectors will take all reasonable measures to ensure that:

- confidential information is not used for any other purpose than the evaluation/inspection activities described in this document; and
- confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they can clearly demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of UNFPA (including disclosure by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of UNFPA (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

4. CONFLICT OF INTEREST

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest.

If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to UNFPA. In this connection each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify UNFPA of any change in this information.
ANNEX I

Prequalification of Contraceptive Devices Letter of Application

All product dossiers and site master files submitted must be accompanied by a cover letter expressing interest in participating in the UNFPA prequalification process and confirming that the information submitted in the Summary Technical Documentation (STED) summary is complete and correct. Below is an example of such a letter.

Letter of Application

Date ………………………..

To: United Nations Population Fund Procurement Services Branch Marmorvej 51 DK 2100 Copenhagen 0 Denmark

Sir/Madam:

Being duly authorized to represent and act on behalf of [name of manufacturer] (hereinafter referred to as the “Applicant”) and having reviewed and fully understood all the information on prequalification provided, the undersigned hereby applies to be prequalified by UNFPA as potential suppliers of [indicate relevant device].

Attached to this letter are copies of original documents defining:

- the Applicant’s legal status
- the Summary Technical Documentation (STED)
- Sample products (if applicable).

UNFPA and its authorized representatives are hereby authorized to conduct any enquiries or investigations to verify the statements, documents and information submitted in connection with this application and to seek clarification from our bankers and clients regarding any financial and technical aspects. This Letter of Application will also serve as authorization to any individual or authorized representative of any institution referred to in the supporting documentation to provide such information deemed necessary and requested by yourselves to verify statements and information provided in this application or with regard to the resources, experience and competence of the Applicant.
The Applicant declares that all the information provided with the application is valid.

Name of Applicant [Organization] _________________________________

Name of Responsible Officer _________________________________

Signature _________________________________

Position/Title _________________________________ Date __________________
ANNEX II

International Standards


|--------------------|---------------------------------------------------------------------|

<table>
<thead>
<tr>
<th>Female Condoms</th>
<th>ISO 25841. Female Condoms—Requirements and Test Methods.</th>
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<tr>
<td><strong>Tcu380A - IUD</strong></td>
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<tr>
<td>ISO 7439 Copper-Bearing Intrauterine Contraceptive Devices - Requirements, Tests.</td>
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<tr>
<td>ISO 14001 Environmental Management</td>
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<td>ISO 14971 Medical Devices - Application of Risk Management to Medical Devices.</td>
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<tr>
<td>ISO 10012 Measurement management systems - requirements for measurement processes and measuring equipment.</td>
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<tr>
<td>ISO 10993 Biological Evaluation of Medical Devices - relevant sections as specified</td>
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<tr>
<td>ISO 10993-1. ISO 11135 Medical devices - Validation and Routine Control of Ethylene Oxide Sterilization - relevant sections as specified in ISO 11135-1.</td>
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<tr>
<td>ISO 11137-3 Guidance on Dosimetric Aspects.</td>
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<tr>
<td>ISO 11607 Packaging for Terminally Sterilized Medical Devices - relevant sections as specified in ISO 11607-1.</td>
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<tr>
<td>ISO 19011 Guidelines for Quality and/or Environmental Management Systems Auditing.</td>
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WHO/UNITED NATIONS POPULATION FUND (UNFPA)

TECHNICAL SPECIFICATION FOR

MALE LATEX CONDOMS

(July 2019)

DRAFT FOR COMMENTS

Medicines Quality Assurance working documents will be sent out electronically and they will also be placed on the Medicines website for comments under “Current projects”.  
http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.
WHO/UNITED NATIONS POPULATION FUND (UNFPA)

TECHNICAL SPECIFICATION FOR MALE LATEX CONDOMS

BACKGROUND

Extract from the Fifty-third World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) meeting report:

“Ms Seloi Mogatle and Dr William Potter from the United Nations Population Fund (UNFPA) gave an update on the prequalification guidance for contraceptive devices and condoms at the Fifty-third Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) that took place at the World Health Organization (WHO) headquarters in Geneva, Switzerland, October 2018. The UNFPA had contacted WHO to inquire how best to start a process to update the process of the following texts that were adopted by the ECSPP and published in 2008. The Expert Committee agreed to the importance of updating these materials in view of the changes in the contraceptive field globally over the previous decade. The two organizations committed to work together to bring the documents up-to-date. It was suggested by UNFPA to separate out the current existing procedure for condoms to include the following aspects:

5. Condom Quality Assurance and Annexes.
7. Condom Storage and Transportation.

UNFPA also raised the issue of specifications for lubricants (both water-based and silicon-bases) which needs to be considered when developing the new guidelines. The Expert Committee supported the development of the relevant documents in consultation with the WHO Secretariat, the preparation of these for public consultation and took note that they will be reported back to the Expert Committee.”
The following documents are undergoing a public consultation as part of this series:


6. QAS/19.806 - WHO/UNFPA Specifications for Plain Lubricants.

7. QAS/19.807 - WHO/UNFPA Condom Quality Assurance
INTRODUCTION

This section contains the WHO/UNFPA Specification which is suitable for the bulk procurement of male latex condoms for use in social marketing and public-sector programmes for sexually transmitted infections (STI)/HIV prevention and family planning. A summary of the technical basis for the WHO/UNFPA Specification is given in Annex I.

A specification is a statement of the buyer’s requirements and covers all the attributes and features of the product. Many of these requirements, particularly the design features, may be unique to the buyer and not specified in ISO 4074. The buyer’s specification must be a detailed and unambiguous statement of the buyer’s requirements and describe the means by which those requirements can be measured and assessed. The specification is generally attached to the Bidding Documents and forms part of the supply contract.

The WHO/UNFPA Specification is based on the performance requirements for male latex condoms specified in the International Standard ISO 4074 Natural Latex Rubber Condoms - Requirements and Test Methods. This standard specifies the essential performance requirements that latex condoms are expected to meet and the test methods that are used to assess compliance with these requirements. This standard is based on extensive research and an ongoing consultation process involving leading experts from around the world in all aspects of condom manufacturing, testing, research and use. The WHO/UNFPA Specification described here incorporates the performance requirements of ISO 4074.

The WHO/UNFPA Specification has been developed by consensus and is based on available evidence, details of which are given in Annex I. The WHO/UNFPA Specification describes the general, design, performance and packaging requirements for the product and the methods of verification. It can be used unchanged or adapted to the specific requirements of programmes. It is important to understand, however, that:

- **General requirements** specify the safety of constituent materials and other characteristics, such as shelf-life. These properties should not vary from lot to lot and therefore do not need testing on a regular basis. Retesting is required following any significant change to the formulation, manufacturing process, equipment used and packaging. The general requirements detailed in the WHO/UNFPA Specification **should not be changed**. They are listed in clause 2.1 of this document.
Performance requirements specify the essential performance attributes of the condoms, established in accordance with ISO 4074. These must be tested on a lot-by-lot basis since the quality of these attributes may vary due to the manufacturing process. Laboratory tests are carried out to assess the barrier properties of the package, the integrity of the product and its ability to resist breakage. Performance requirements detailed in the WHO/UNFPA Specification should not be changed. The only exceptions are:

- The possibility to include or exclude bursting volume and pressure testing after oven conditioning;
- The packaging integrity requirements where the purchaser may choose to apply more stringent testing, especially if the condoms are to be delivered by air or to high altitude locations (refer to alternate package seal integrity test in Annex 2).

The performance requirements are listed in clause 2.2 of this document.

Design requirements are mainly concerned with the acceptability of the product to the end-user. These can be varied within certain limits to meet specific programmatic requirements. Special boxes have been provided in the WHO/UNFPA Specification for changes to such design requirements as colour, length and width. For each design requirement, there is a means of verification. These are listed in clause 2.3 of this document.

Packaging requirements are detailed in the WHO/UNFPA Specification. Packaging materials and package shape should not be changed unless the impact on the shelf-life of the product has been confirmed by accelerated stability studies and real time stability studies are in progress according to clause 11 ISO 4074.:2015. If consumer packaging is required, it is important to include detailed instructions in the specification and to discuss the design requirements with the manufacturer. The packaging requirements are listed in clause 2.2 of this document.

The WHO/UNFPA Specification is based on:

- the International Standard ISO 4074;
- a literature review of the available evidence;
- the recommendations of the WHO/UNFPA/UNAIDS/FHI360 Male Latex Condom Technical Review Committee (May 2002, August 2007 and July 2008); and
- feedback from participants attending the WHO/UNFPA workshops to introduce the male latex condom specification, prequalification and procurement procedures.
Where appropriate, reference is made to the current edition and corrigenda of the published International Standard, ISO 4074 Natural Latex Rubber Condoms.

This WHO/UNFPA Specification should not be considered nor used as a standard for regulatory purposes. For regulatory purposes, the applicable standard is ISO 4074 or the relevant local standard, depending on country.

The WHO/UNFPA Specification, if used in conjunction with the WHO/UNFPA Prequalification Programme will ensure that a quality assured product is prequalified and later purchased and distributed to the end-user.

2. WHO/UNFPA SPECIFICATION

2.1 General requirements

Manufacturers shall include in their Summary of Technical Documentation, evidence to confirm that the condoms comply with the General Requirements listed in Table 1. Verification of conformance to these requirements is assessed during prequalification.

General Requirements cover the selection and safety of materials and the shelf-life of the product.

Condoms shall comply with the Performance Requirements of this WHO/UNFPA Specification throughout the stated shelf-life of the condom. Manufacturers must determine the shelf-life by real-time studies conducted at (30 ± 2) °C. Pending the outcome of real-time studies, manufacturers may use accelerated studies at (50 ± 2) °C to estimate a provisional shelf-life.

ISO 4074 describes minimum stability requirements for condoms. These are considered the minimum requirements for placing condoms on the market. It can be assumed that condoms meeting these requirements have a minimum shelf-life of two years. Data supporting compliance with the Minimum Stability Requirements can be extracted from accelerated ageing (stability) studies. Manufacturers may wish to use the minimum stability test as a screening procedure during product or process development.

UNFPA requires confirmation that condoms comply with the minimum stability requirements specified in ISO 4074 during prequalification by testing condoms that have been oven conditioned for (168 ± 5) hours at (70 ± 2) °C.
### Table 1. General requirements of condoms

<table>
<thead>
<tr>
<th>General requirements</th>
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<tbody>
<tr>
<td><strong>Lot definition</strong></td>
<td>A lot is a collection of condoms of the same design, colour, shape, size and formulation. A lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing, and be packed in the same type of individual container, using the same packaging materials. All condoms comprising a LOT will:</td>
</tr>
<tr>
<td></td>
<td>• have an identical formulation;</td>
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<tr>
<td></td>
<td>• have the same design, dimensions, colour, shape and surface texture;</td>
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<tr>
<td></td>
<td>• be manufactured on the same production line;</td>
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<tr>
<td></td>
<td>• be vulcanized under identical conditions;</td>
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<td></td>
<td>• be in the same packaging;</td>
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<tr>
<td></td>
<td>• have the same lubricant; and</td>
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<td></td>
<td>• have the same date of expiry printed on the package.</td>
</tr>
<tr>
<td></td>
<td>LOT sizes over 500,000 are not permitted.</td>
</tr>
<tr>
<td><strong>Date of manufacturer</strong></td>
<td>The date of manufacture is generally the date that the condoms were dipped.</td>
</tr>
<tr>
<td></td>
<td>The date of manufacture may be the date of packaging (i.e. sealing the condoms into the individual containers) as long as the storage period between dipping and packaging does not exceed 6 months and the unpackaged condoms are stored under controlled conditions as specified in Clause 11.1 of ISO 4074:2015. Storage conditions will be subject to assessment as part of the prequalification inspection.</td>
</tr>
<tr>
<td><strong>Materials</strong></td>
<td>The condoms shall be made of natural rubber latex.</td>
</tr>
<tr>
<td></td>
<td>The condoms shall not liberate toxic or otherwise harmful substances in amounts that can be irritating, sensitizing or otherwise harmful to the user of the condom under normal conditions of use.</td>
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</tbody>
</table>
| Biocompatibility | Biocompatibility assessments shall be conducted on the whole condom, including any lubricants and dressing materials, in accordance with ISO 10993–1. Specifically, evaluations shall be conducted for cytotoxicity according to ISO 10993–5 and for irritation and sensitization according to ISO 10993–10. Manufacturers should choose accredited laboratories for these tests, and the results shall be interpreted by an accredited toxicologist or other suitably qualified expert. Expert reports should be available for review. The expert review report can be a separate document or can be included in the test report. Extraction conditions shall be at a temperature of 37 ± 1, according to ISO 10993-12.

Many latex products that have been established as safe, including condoms and medical gloves, can exhibit a positive cytotoxic response when tested according to ISO 10993-5. While any cytotoxic effect can be of concern, it is primarily an indication of potential for in vivo toxicity and a condom cannot necessarily be determined to be unsuitable for use based solely on cytotoxicity data.

Manufacturers are advised to confirm local requirements for safety testing with appropriate regulatory authorities in the countries in which the condoms are to be distributed. In accordance with ISO 10993–1, manufacturers may provide data on equivalent products.

The International Agency for Research on Cancer (IARC, WHO) has classified 2-mercaptobenzothiazole (MBT) as probably carcinogenic to humans (IARC Monograph 115 March 2016). MBT shall not be used as an accelerator in condom formulations |
| **Water-extractable protein levels** | It will be verified during prequalification that manufacturers determine the water-extractable levels of proteins in their products.

The recommended levels for soluble protein, as determined by the modified Lowry method, should be less than 200 µg/g. Manufacturers should take steps not to exceed this level and should monitor production periodically, at least once a year and following any significant change to the latex formulation. The recommended interval is every three months.

There is no specific standard for determining the protein levels in condoms. The methods described in ISO 12243 or EN 455–3 or ASTM D5172 for determining the protein levels in medical gloves can be modified for condoms.4

Documentation recording protein levels should be available for review. |
| **Bioburden levels** | Condoms are not sterile devices, but nevertheless manufacturers should take steps to minimize the risk of contamination of the products with micro-organisms. It will be verified during prequalification that manufacturers periodically determine bioburden levels. Documentation recording bioburden levels should be available for review.

For prequalification, the manufacturer should be able to demonstrate that they are able to maintain bioburden levels on packed condoms below 100 cfu and not exceeding 500 cfu. There should be an absence of Staphylococcus aureus and Enterobacteriaceae including Escherichia coli and Pseudomonas aeruginosa.

For prequalification, bioburden levels should be determined periodically, e.g. at least quarterly (and following any significant change to the latex formulation), by extracting the condoms with a neutralizing medium and determining the total viable aerobic count using appropriate test methods. Further information on the rationale for the bioburden limits, methods of determining |

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4 For further information about latex allergy and protein levels, refer to Annex 1.
### Nitrosamines

It will be verified during prequalification that manufacturers take steps to minimize the formation of nitrosamines. For prequalification purposes, the manufacturer should be able to demonstrate they are able to achieve levels below 50 ppb measured as per ISO 29941. Levels should be monitored periodically and at least once a year, and following and significant change to the latex formulation.

Minimizing the formation of nitrosamines can be done by ensuring that condoms are adequately leached and washed by using minimum amounts of accelerators. It is recommended that, where possible, accelerators, such as zinc dibutyldithiocarbamate, that have a preferred safety profile\(^5\), are used in the formulation.

### Dusting powder

A suitable dusting powder should be used to prevent the condoms from sticking together during manufacture. Acceptable powders are:
- cornstarch;
- magnesium or calcium carbonate; and
- silica.

Manufacturers may use other dusting powders as long as they do not compromise the biocompatibility and safety of the condom.

Talc or lycopodium spores shall not be used.

It is recommended that manufacturers not use excess powder (maximum recommended is 50 mg per condom).

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<table>
<thead>
<tr>
<th><strong>Sheelf-life and stability studies requirement</strong></th>
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<tr>
<td><strong>Shelf-life</strong></td>
</tr>
<tr>
<td>Condoms shall comply with the performance requirements of this WHO/UNFPA Specification throughout the stated shelf-life of the condom. The manufacturer shall determine the shelf-life based on the outcome of stability studies and measured from the date of manufacture. The date of manufacture is generally the date that the condoms were dipped.</td>
</tr>
<tr>
<td>The claimed shelf-life shall be not less than three years and not more than five years.</td>
</tr>
<tr>
<td>Shelf-life shall be determined on condoms that have been stored for the maximum period of time between dipping and foiling that is permitted in the standard operating procedures of the manufacturer. For WHO/UNFPA prequalified manufacturers, the maximum period of time between dipping and foiling is 6 months, but manufacturers may use shelf-life data from stability studies with condoms that have been stored up to two years prior to packaging as specified ISO 4074:2015 to support shelf-life claims.</td>
</tr>
<tr>
<td><strong>Variations</strong></td>
</tr>
<tr>
<td>Textured condoms should be subjected to accelerated stability studies extending out to 180 days at 50°C but can be purchased initially on the basis of data covering 7 days at 70°C and 90 days at 50°C.</td>
</tr>
<tr>
<td><strong>Stability studies – real time</strong></td>
</tr>
<tr>
<td>Shelf-life shall be confirmed by real-time stability studies conducted at (30 ±5 ±2) °C 3 according to the relevant clause in ISO 4074. Pending the outcome of the real-time studies, manufacturers may estimate a provisional shelf-life using an accelerated ageing study6.</td>
</tr>
<tr>
<td>Results of an accelerated aging study, according to ISO 4074, must be available at the time of submitting an application for prequalification, and a real time study must also be in progress.</td>
</tr>
<tr>
<td><strong>Sampling</strong></td>
</tr>
<tr>
<td>Condom for stability studies shall be taken from three normal production lots. Sampling shall be done according Annex A or Annex B (preferred) of ISO 4074. Sample size should be adequate for at least 6 separate tests for the three tests from ISO 4074.</td>
</tr>
</tbody>
</table>

---

6 As described in ISO 4074
<table>
<thead>
<tr>
<th><strong>Conditioning</strong></th>
<th>Condition condoms at ((30 \pm 5) , ^\circ C) in accordance with the relevant annex of ISO 4074.</th>
</tr>
</thead>
</table>
| **Testing requirement** | Assess compliance with the requirements for bursting properties at least annually for the full shelf-life of the product and for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074 by the end of the testing period. 

All three lots of condoms shall remain in compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074 for the duration of the stability study. 

If at any time during the real-time studies the manufacturer becomes aware that the shelf-life estimates made using the accelerated studies are incorrect, the manufacturer must notify the procurers and regulators immediately. |
| **Provisional shelf-life** | Pending the outcome of the real-time studies, manufacturers may estimate a provisional shelf-life using an accelerated ageing study. |
| **Sampling** | Sample condoms from three manufacturing lots in accordance with Annex A or B (preferred) of ISO 4074. |
| **Conditioning** | Condition condoms at \((50 \pm 2) \, ^\circ C\) for 120 days or 180 days in accordance with the relevant annex of ISO 4074. |
| **Testing requirement** | Assess compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074. 

If all three lots of condoms remain in compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074 for a period of 120 days at \((50 \pm 2) \, ^\circ C\), a provisional shelf-life of three years may be assigned. 

If all three lots of condoms remain in compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074 for a period of 180 days at \((50 \pm 2) \, ^\circ C\), a provisional shelf-life of five years may be assigned. |
| **Minimum stability requirements** | Condoms shall comply with the minimum stability requirements defined in the relevant clause of ISO 4074. Condoms meeting these minimum stability requirements can be assumed to have a provisional shelf-life of two years. |
| **Sampling** | Three lots sampled in accordance with ISO 2859–1 and Annex A or B (preferred) of ISO 4074. |
| **Conditioning** | Incubate samples in their individual sealed containers according to the relevant annex of ISO 4074: |
| &nbsp; | One set for 168 ± 2 hours at (70 ± 2) °C, and another set for (90 ± 1) days at (50 ± 2) °C. |
| &nbsp; | At the end of the incubation periods, withdraw the condoms and test for airburst properties, freedom from holes and package seal. |
| &nbsp; | The incubation period at (50 ± 2) °C can be extended to 120 or 180 days in order to estimate a provisional shelf-life by accelerated ageing, in which case testing at 90 days is not necessary. |
| **Testing requirement** | All three lot of condoms shall remain in compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074. |
| **Stability study report** | The stability study reports should indicate the time between dipping and foiling for the lots used for the study. If a manufacturer has not recorded the required information in the stability study report, then the default position will be that the manufacturer must use the dipping date as the date of manufacture. |

### 2.2 Performance requirements

The performance requirements specified here are based on the requirements of ISO 4074. These requirements cannot be altered. Verification of compliance with these requirements must be done as part of prequalification and the lot-by-lot Pre-shipment compliance testing of the product. For prequalification purposes, the sampling plans specified in Annex B of ISO 4074 shall be used. Testing after oven conditioning may be required as part of prequalification following a risk based assessment.

Information on methods of monitoring quality is given in the Condom Quality Assurance guidance document.
### Table 2: Performance requirements

<table>
<thead>
<tr>
<th>Performance requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bursting volume and pressure</strong></td>
</tr>
<tr>
<td><strong>Sampling</strong></td>
</tr>
<tr>
<td>In accordance with ISO 2859–1 General Inspection Level I.</td>
</tr>
<tr>
<td>For prequalification testing, at least Code Letter M as specified in Annex B of ISO 4074 shall be used.</td>
</tr>
<tr>
<td><strong>Testing</strong></td>
</tr>
<tr>
<td>In accordance with test method in the relevant annex of ISO 4074 and the relevant clause in ISO 4074.</td>
</tr>
<tr>
<td><strong>Requirement</strong></td>
</tr>
<tr>
<td>Minimum bursting requirements as listed below:</td>
</tr>
<tr>
<td>AQL 1.5</td>
</tr>
<tr>
<td><strong>Volume:</strong></td>
</tr>
<tr>
<td>- 16.0 dm$^3$ for condoms with mid body widths greater than or equal to 45.0 mm and less than 50.0 mm;</td>
</tr>
<tr>
<td>- 18.0 dm$^3$ for condoms with mid body widths greater than or equal to 50.0 mm and less than 56.0 mm;</td>
</tr>
<tr>
<td>- 22.0 dm$^3$ for condoms with mid body widths greater than or equal to 56.0 mm and less than 65.0 mm; and</td>
</tr>
<tr>
<td>- 28.0 dm$^3$ for condoms with mid body widths greater than or equal to 65.0 mm and not more than 75.0 mm.</td>
</tr>
<tr>
<td><strong>Pressure:</strong> 1.0 kPa (for all widths)</td>
</tr>
</tbody>
</table>

The width is defined as the mean lay-flat width of 13 condoms measured in accordance with the relevant annex of ISO 4074 at a point (75 ± 5) mm from the closed end, rounded to the nearest 0.5 mm.

<table>
<thead>
<tr>
<th>Freedom from holes and visible defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sampling</strong></td>
</tr>
<tr>
<td>ISO 2859–1 General Inspection Level I, but at least Code Letter M.</td>
</tr>
<tr>
<td>For prequalification testing, at least Code Letter N as specified in Annex B of ISO 4074 shall be used.</td>
</tr>
<tr>
<td><strong>Testing</strong></td>
</tr>
<tr>
<td>In accordance with the relevant annex of ISO 4074.</td>
</tr>
</tbody>
</table>
In accordance with test method in the relevant annex of ISO 4074.

| Requirement            | Freedom from holes: **AQL 0.25**  
|                        | Critical visible defects: **AQL 0.4**  
|                        | Visibly open package seals: AQL 0.4  

ISO 4074 describes a limited number of critical visible defects. WHO/UNFPA specifies an extended list of critical visible defects and imperfections in clause 2.2.1.1

It is not possible to define all critical defects and imperfections, and it may be necessary to exercise some judgement about whether or not a particular visible defect is critical. (If you need assistance, contact qa-team-group@unfpa.org.)

If the visible defect may affect the performance of the condom, the defect is considered critical. If a defect not listed in Table 3 is considered critical by any party, then the procurer, test laboratory and manufacturer must consult with each other to agree on the classification of the defect concerned.

Exact definitions of critical defects and imperfections should be reviewed and agreed upon during the contractual process.

| Package seal integrity | **Sampling** | ISO 2859–1 Inspection Level S-3.  
|                       | **Testing** | In accordance with the package integrity test method in the relevant annex of ISO 4074.  
|                       | **Requirement** | AQL 2.5  

**Alternative package seal integrity method** - (for condoms to be delivered by air shipment or to high altitude destinations), to be specified in contracts. To be adopted and manufacturers given transition period: 6 months to 1 year of publishing of this specification

| Sampling | ISO 2859–1 Inspection Level S-3.  
| Testing | (To be described.). Strip and individual packs to be made clear.  
| Requirement | **AQL 2.5**  

Over a transition period of 6 months to 1 year, the AQL will be tightened to 1.0, then to 0.4
2.2.1 Types of visible defects

2.2.1.1 Critical visible defects

Some visible defects may adversely affect the performance of the condom, for example by increasing the risk of them breaking or slipping off in use. These defects are classified as critical and an AQL of 0.4 is applied to non-conforming condoms.

The most common critical visible defects are covered by ISO 4074. These defects include broken, missing or severely distorted beads and permanent creases with adhesion of the film. They are evaluated by visual inspection as part of the procedure for testing for freedom from holes.

Other types of critical visual defects are occasionally seen, and they should be assessed for their potential effect on the performance and acceptability of the condom.

Some of the more common critical visible defects are described in Table 3 and imperfections are listed in Table 4.

Table 3. Critical visible defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleat/crease</td>
<td>The film sticks to itself and the pleat/crease cannot be removed by gently stretching of the adjacent film.</td>
</tr>
<tr>
<td>Blister/bubble</td>
<td>An obvious circular or teardrop-shaped thin area with a well-defined border in the film. (Such defects may break under pressure.)</td>
</tr>
<tr>
<td>Embedded and surface particles</td>
<td>Any particle with any dimension of 1 mm or greater. These may be dirt, hair, insects, powder granules, coagulum, etc.</td>
</tr>
<tr>
<td>Bead defects</td>
<td>Faulty, missing or severely distorted beads (as in ISO 4074).</td>
</tr>
<tr>
<td>Crack marks</td>
<td>Lines that penetrate the surface of the film, formed by shrinkage of the latex during drying. These do not include flow lines or marks from the mould.</td>
</tr>
<tr>
<td>Delamination</td>
<td>Areas where the individual layers of latex separate. (Condoms are formed by two or more dips in the liquid latex.)</td>
</tr>
<tr>
<td>Thin areas</td>
<td>Small areas of the condom (including the teat) that are visibly thin. These can show up as bulges with well-defined edges on the freedom-from-holes test. Condoms that look asymmetrical when filled with water are not in this category (see Table 6).</td>
</tr>
<tr>
<td>“Cupping” (a concave region at the end of the teat)</td>
<td>An apparent indentation at the end of the teat which is often caused by significant thickness variations around the teat. Very small concave areas (&lt;2 mm) shall be treated as non-critical visible defects. Small areas including teat.</td>
</tr>
</tbody>
</table>
Table 4. Imperfections that are not regarded as defects

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-coagulum</td>
<td>Particles of rubber with dimensions less than 1 mm.</td>
</tr>
<tr>
<td>Flow lines</td>
<td>Lines of denser material in the film.</td>
</tr>
<tr>
<td>Small concave spot at end of teat</td>
<td>An apparent indentation caused during the withdrawal of the former (dipping mould) from the latex. Large concave spots (e.g. &gt; 2 mm) at the end of the teat shall be treated as thin areas (critical visible defect).</td>
</tr>
<tr>
<td>Distortion due to rolling</td>
<td>Apparent variations in condom width due to stretching during rolling.</td>
</tr>
<tr>
<td>Distortion when testing for freedom from holes</td>
<td>Distortion of the condom during the freedom-from-holes test that are due to small differences in thickness around the wall of the condom caused by relative movement of the latex and the former (dipping mould) during dipping (bulges with well-defined edges should be treated as critical visible defects).</td>
</tr>
<tr>
<td>Uneven lubricant</td>
<td>The open end of the condom may appear dry, especially on new condoms. The lubricant penetrates the roll slowly.</td>
</tr>
<tr>
<td>Embedded and surface particles (small)</td>
<td>Particles with dimensions less than 1 mm that are visible to the naked or corrected eye.</td>
</tr>
<tr>
<td>Faulty bead (minor)</td>
<td>Uneven and partially distorted beads.</td>
</tr>
<tr>
<td>Uneven colour</td>
<td>Minor streaking.</td>
</tr>
</tbody>
</table>

2.2.2 Packaging defects and ISO 4074

The main packaging defects are listed in Table 5. Additional defects are sometimes detected only after shipment. This section summarizes common types of packaging defects, including those detailed in the WHO/UNFPA Specification.

Individual packages

The quality of the individual foil packages shall be assessed by visual inspection using a sampling plan in accordance with ISO 2859–1 Inspection Level S-3. An AQL of 2.5 shall be applied to these defects collectively. Packaging defects are summarized in Table 5.
**Consumer packs**

There are no requirements for consumer packs included in the WHO/UNFPA Specification. Procurers should fully specify requirements in accordance with programme needs. Compliance should be assessed by visual inspection using a sampling plan in accordance with ISO 2859–1 Inspection Level S-3. It is recommended that an AQL of 2.5 be applied to consumer pack requirements.

In cases where organizations repack condoms into consumer packaging, the quality of the consumer packaging is entirely at the discretion of the organization doing the repacking. The only requirements that can be specified are the labelling requirements for the consumer pack and information to be supplied to the user. These requirements are detailed in ISO 4074:2015, although local requirements may apply as well.

**Cartons and marking**

Packaging Requirements should be agreed in the purchase order. Compliance should be assessed by visual inspection, using a sampling plan in accordance with ISO 2859–1 Inspection Level S-3. It is recommended that an AQL of 4.0 be applied to carton requirements.

**Table 5. Packaging defects**

<table>
<thead>
<tr>
<th>Individual foil packaging defects</th>
<th>Inspection Level S-3. An AQL of 2.5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty package.</td>
<td>Missing manufacturer’s name.</td>
</tr>
<tr>
<td>No lubricant.</td>
<td>Incorrect/missing lot number.</td>
</tr>
<tr>
<td>Lubricant leakage.</td>
<td>Incorrect/missing manufacture date.</td>
</tr>
<tr>
<td>Delamination of the packaging film.</td>
<td>Incorrect/missing expiry date.</td>
</tr>
<tr>
<td>Discoloured film and labels.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consumer packs</th>
<th>Inspection Level S-3. An AQL of 2.5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing manufacturer’s name.</td>
<td>Empty or partially filled packs.</td>
</tr>
<tr>
<td>Incorrect/missing lot number.</td>
<td>Discolouration.</td>
</tr>
<tr>
<td>Incorrect/missing date of manufacture.</td>
<td>Delamination.</td>
</tr>
<tr>
<td>Incorrect/missing expiry date.</td>
<td></td>
</tr>
<tr>
<td>Incorrect format of expiry date.</td>
<td></td>
</tr>
</tbody>
</table>
Cartons and markings

**Inspection Level S-3. An AQL of 4.0.**

<table>
<thead>
<tr>
<th>Missing manufacturer’s name.</th>
<th>Non-permanent marking.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect/missing lot number.</td>
<td>Empty or partially filled cartons.</td>
</tr>
<tr>
<td>Incorrect/missing manufacture date.</td>
<td>Damaged cartons that may affect the integrity or quality of the condoms inside.</td>
</tr>
<tr>
<td>Incorrect/missing expiry date.</td>
<td></td>
</tr>
</tbody>
</table>

### 2.3 Design requirements

The design properties listed in Table 6 may be adapted, where appropriately indicated, to reflect the specific needs of the programme and population of intended users. Modification should be based on information about the target population. Verification of compliance with these requirements is to be done as part of the lot-by-lot compliance testing of the product.

If specific design changes are agreed between manufacturer and procurer, then any appropriate testing procedures and sampling plans and compliance levels (AQLs) should also be agreed. Changes in condom design, such as different shapes or the inclusion of pigments, can affect airburst properties and, in some circumstances, freedom from holes.

It is recommended that, where changes to the specification are made, dimensional requirements and design features should be subject to ISO 2859-1 Inspection Level S-2 with an AQL of 1.0.

Appropriate reference samples should be maintained by the manufacturer and testing laboratory. The national regulatory authority and/or purchaser may also retain reference samples.

**Table 6. Design requirements**

<table>
<thead>
<tr>
<th>Shape and texture</th>
<th>The surface of the condoms can be textured or non-textured. Texturing typically consists of a number of ribs or dots formed onto the surface of the condom.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verify by visual inspection</strong></td>
<td>Condoms may be of any shape consistent with normal commercial practice and client requirements. If the condom is not parallel-sided and smooth, attach a dimensioned drawing with detailed description, which should be agreed with by manufacturer and procurer.</td>
</tr>
</tbody>
</table>

### Integral bead

**Verify by visual inspection**

The open end of the condom shall have a rolled ring of latex, called an integral bead, “rim” or “ring”.

### Colour, to be evaluated at prequalification

**Verify by visual inspection**

Condoms can be translucent, pigmented or unpigmented.

Pigments used with coloured condoms shall be suitable for use in medical devices and shall not degrade the rubber. Shelf-life verified by accelerated stability studies verified at 90 days and 180 days at 50 centigrade.

If a pigment is required, indicate the colour and provide full details of the pigment, including a Material Safety Data Sheet (MSDS).

Pigments and pigment dispersions or flavours used with coloured condoms shall be suitable for use in medical devices. The condom and pigment and flavours and fragrances shall be subject to biocompatibility evaluation according to ISO 10993.

For verification purposes, 180 days at 50°C for 3 lots – data to be generated and submitted by manufacturer if not available at time of prequalification (provisional prequalification can be based on 7 days at 70°C).

### Odour and fragrance to be evaluated at prequalification

**Verify by visual inspection and smell**

The condoms shall not give off an unpleasant odour when the package is opened at any time after manufacture and for the shelf-life of the product. It is recommended that manufacturers include odour assessment as part of their shelf-life studies. (Condoms have a characteristic odour of rubber which tends to dissipate quickly once the package is opened. A mild odour that dissipates quickly is acceptable.)

Procurers may specify the addition of a suitable fragrance. Such fragrances must be non-toxic, non-irritant and not degrade the rubber. The manufacturer shall supply details of the fragrance used and the amount added to the procurer. Fragrances used with condoms shall be suitable for use in medical devices. The condom and fragrance shall be subject to biocompatibility evaluation according to ISO 10993-1. The shelf-life of any fragranced condom shall be verified as described in section 2.1 “General Requirements”.
If a fragrance is desired, the manufacturer should specify it and provide full details of the fragrance, including an MSDS.

<table>
<thead>
<tr>
<th><strong>Testing</strong></th>
<th>See Annex III for guidance on odour testing. If a masking agent or fragrance is used, odour testing should become part of the lot-by-lot Pre-shipment compliance testing. Odour testing should be included in ageing studies.</th>
</tr>
</thead>
</table>

### Width

<table>
<thead>
<tr>
<th><strong>Sampling</strong></th>
<th>In accordance with <em>ISO 2859–1</em> Inspection Level S-2.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
<td>In accordance with the test method in the relevant annex of <em>ISO 4074</em>.</td>
</tr>
<tr>
<td><strong>Requirement</strong></td>
<td>The width is defined as the mean lay-flat width of 13 condoms measured in accordance with the relevant annex of <em>ISO 4074</em> at a point (35 ± 15) mm from the open end, rounded to the nearest 0.5 mm. Standard widths within the public sector are 49 mm and 53 mm, with a tolerance of ± 2 mm.</td>
</tr>
</tbody>
</table>

**AQL 1.0**

Other widths are available and may be more appropriate for specific target populations described in Annex I. Users should select the appropriate width based on the best available data on the target population.

### Length

<table>
<thead>
<tr>
<th><strong>Sampling</strong></th>
<th>In accordance with <em>ISO 2859–1</em> Inspection Level S-2.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
<td>In accordance with the test method in the relevant annex of <em>ISO 4074</em>.</td>
</tr>
<tr>
<td><strong>Requirement</strong></td>
<td>A minimum of 165 mm for condoms with nominal widths less than 50.0 mm. A minimum of 180 mm for condoms with nominal widths from 50.0 mm up to 55.5 mm. A minimum of 190 mm for condoms with nominal widths equal to or greater than 56.0 mm.</td>
</tr>
</tbody>
</table>

**AQL 1.0**
<table>
<thead>
<tr>
<th>Thickness</th>
<th>In accordance with ISO 2859–1 Inspection Level S-2.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling</td>
<td>In accordance with the test method in the relevant annex of ISO 4074.</td>
</tr>
</tbody>
</table>
| Testing   | Unless otherwise specified, the nominal thickness will be 0.065 mm. If a different thickness is specified, then this must be agreed between the procurer and manufacturer. The thickness shall be stated in the specification and any purchase orders. The average single-wall thickness calculated for the 13 condoms tested shall be equal to the specified nominal thickness subject to a tolerance of:

± 0.008 mm for condoms with nominal specified thickness less than 0.05 mm;

± 0.01 mm for condoms with nominal claimed thickness equal to or greater than 0.05 mm.

AQL 1.0

If a micrometer gauge is used, the thickness measurements are taken at three locations around the circumference of the condom at 30 ± 5 mm from the open end, 30 ± 5 mm from the closed end (excluding the reservoir tip), and at the mid-distance between those two points. The condom thickness is reported as the mean of the 9 measurements. For partially textured condoms the thickness shall be measured at points closest to those specified above where the surface is smooth. The locations of the points of measurement shall be noted.

If it is not possible to locate a smooth region on the condom where thickness can be measured, then thickness shall be measured at the points specified above and the specification should be adjusted to allow for the effect of the texturing—for example, by reference to the manufacturer’s specification. In such cases the method of measurement should be specified (gauge or ring weight).

It should be noted that the mass method when used for textured condoms, gives the approximate average for thickness, as opposed to the micrometer method, which gives an estimate.
Condoms thicker than 0.080 mm are usually considered to be extra thick, whereas condoms that are thinner than 0.060 mm are usually considered to be thin. There is no evidence that extra thick condoms (sometimes called extra strong) provide additional protection.

### Quantity of lubricant including powder

<table>
<thead>
<tr>
<th>Metric</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sampling</strong></td>
<td>In accordance with <em>ISO 2859–1</em> Inspection Level S-2.</td>
</tr>
<tr>
<td><strong>Testing</strong></td>
<td>In accordance with the test method in the relevant annex of <em>ISO 4074</em>.</td>
</tr>
<tr>
<td><strong>Requirement</strong></td>
<td>The condom shall be lubricated with a quantity of silicone fluid having a nominal viscosity between 200 and 350 centistokes. Other lubricants such as glycols and water-based lubricants may be used by agreement between manufacturer and procurer. Oil-based lubricants should NOT be used. The nominal quantity of lubricant, including powder, in the package should be in the range 350 mg to 600 mg. The quantity of lubricant may be varied depending upon local requirements. UNFPA recommend 450 mg as the nominal dose but lower quantities may be appropriate for some markets. The nominal quantity of lubricant must be agreed between the procurer and manufacturer. The agreed nominal quantity of lubricant shall be stated in the specification and any purchase orders. The amount of lubricant, including any dusting powder, shall be equal to the specified nominal amount within a tolerance of ± 100 mg. If no amount is indicated the nominal amount of lubricant shall be 450 mg.</td>
</tr>
</tbody>
</table>

**AQL 4.0**

### Individual package materials and markings

<table>
<thead>
<tr>
<th>Metric</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Sometimes referred to primary packaging, individual packaging or individual containers</td>
</tr>
<tr>
<td><strong>Packaging requirement</strong></td>
<td>The colour, print design and identification markings, including Pantone references and font sizes, shall be as specified by the buyer and annexed to the specification for the purchase order. Unless otherwise specified, the individual packages shall be square or circular and shall not distort the rolled condom. The package shall be hermetically sealed and shall protect the product from oxygen, ozone, water vapour, ultraviolet and visible light</td>
</tr>
</tbody>
</table>
The package shall be hermetically sealed and shall protect the product from oxygen, ozone, water vapour, ultraviolet and visible light. If an alternative package shape is specified, then the shelf-life of the product in that package shall be confirmed as described in section 2.1 General requirements.

**AQL 2.5**

<table>
<thead>
<tr>
<th>Labelling requirement</th>
<th>The individual package shall have the following markings:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- manufacturer’s name; and identification(address) of manufacturing site*</td>
</tr>
<tr>
<td></td>
<td>- lot number or lot identification code (printed at the time of packaging, not pre-printed);</td>
</tr>
<tr>
<td></td>
<td>- expiry date: Month and year in language(s) to be specified by the procurer. The year shall be written as a four-digit number and the month as a two-digit number (YYYY-MM) (printed at the time of packaging, not pre-printed).</td>
</tr>
</tbody>
</table>

Other information, including texture, colour and fragrance can be agreed on between manufacturer and procurer. If such cases, it is recommended that pre-printed foil is used.

*Note: If dipping of the condoms is done on one site and the naked condoms are packed and released for testing on another site, it is the manufacturer name and manufacturing site that the did the final release testing that should be printed.

**Manufacturing date: Month-and-year manufacturing date can be added if required by procurer.**

**The lot numbers on packages must be printed at the time of packaging.**

Sampling

In accordance with *ISO 2859* Inspection Level S-2.

Testing

The sample of condom packages is visually inspected to verify the required aspects of package quality.

Verified by visual inspection

Shape: Unless otherwise specified, the individual packages shall be square or circular and shall not distort the rolled condom. The printing requirements, packaging and labelling can be verified by visual inspection.
### Verified by supplier’s data or independent test

Material - verified by manufacturer’s data.

If it is not specified, packages should be constructed of a laminate, which includes a layer of suitable impermeable flexible aluminium foil (recommended minimum thickness of 8 micrometres) and layers of plastic materials suitable for the mechanical protection of the metal foil and for printing and sealing.

The lot numbers on packages must be printed at the time of packaging.

**In addition, the following shall apply:**

- There shall be no evidence of leakage.
- The outside surface of the package shall be clean.
- There shall be no separation of the layers of laminate.
- If the sealed packages are in strips, the individual packages are separated by perforations or other means that allow the packages to be separated by hand without interfering with the seals.
- The package must be easy to open without damaging the condom.

### Alternate package materials

Alternative package materials can be accepted if they have barrier and strength properties comparable to those of the packaging recommended above or if there are real-time stability data to show that the condom in its pack has adequate shelf-life.

If an alternative material is required, append the full specification and mark here: The lot numbers on packages must be printed at the time of packaging.

In addition, the following shall apply:

- There shall be no evidence of leakage.
- The outside surface of the package shall be clean.
- There shall be no separation of the layers of laminate.
- If the sealed packages are in strips, the individual packages are separated by perforations or other means that allow the packages to be separated by hand without interfering with the seals.
- The package must be easy to open without damaging the condom.
References


ANNEX 1

List of relevant international standards relevant to the male latex condom prequalification programme

Various external documents form part of the WHO/UNFPA Specification and the buyer may wish to mention them in any Invitation to Bid or order sent to the supplier. In every case, the edition of the document is the one in force on the date of the Invitation to Bid. These are standards published by the International Organization for Standardization (ISO). The latest version of the standard should be used by manufacturers.

Male Latex Condoms


ANNEX 2

Alternate package seal integrity test

1. **Principle of the dry vacuum method**

The condom packs are washed and dried, wrapped in coloured tissue, and put into U-shaped holders that prevent them from expanding. The U-shaped holders are placed in a vacuum chamber, which is evacuated for 20 minutes. The coloured tissue is examined for signs of staining. The packs are then examined, repacked and passed through the vacuum again, and the tissue re-examined.

Packs are considered to be leaking if:

a. A stain appears on the first examination, and the stain is found to be larger on the second examination.

b. No stain appears on the first examination, and one appears on the second examination.

2. **Equipment required for the dry vacuum method**

The following equipment is required:

a. Ultrasonic cleaners with baths long enough to hold strips of 3 condoms (say, 200 mm). If the baths not long enough, the strips it can be gently folded to fit.

   **Note:** *It is necessary to ensure that the strips are submerged in the bath. This may be done by weighting the samples with a piece of metal (e.g. a large nut) or by using a frame that is part of the bath.*

b. Towels or tissues suitable for drying the packs (4 packs supplied).

c. Isopropanol for washing (technical grade).

d. U-shaped holders for condom strips (10 supplied).

e. Coloured tissue suitable for wrapping the strips in order to show leakage stains (4 packs supplied).
f. Vacuum chamber (e.g. desiccator) capable of holding multiple U-shaped holders.

g. Vacuum pump capable of evacuating the vacuum chamber to 20 kPa (absolute).

*Note:* Manual washing may be used instead of the ultrasonic baths provided that the process is shown to remove lubricant which can be embedded in the stamping of the seals or in the serrations between packs.

### 3. Dry vacuum method

For each Test ID (A, B, C and D):

a. Select 20 strips of 3 condoms each from the samples to be tested.

b. Wash 10 strips in isopropanol in an ultrasonic bath for 10 minutes, and ensure they are submerged (see page 3).

*Note:* The isopropanol can be re-used until it looks dirty on visual examination.

c. Remove the strips from the bath, and dry them with a paper towel.

d. Place the strips on a clean dry paper towel for to air-dry for at least 10 minutes.

e. Ensure the strips are dry, then mark each individual strip with a reference number from 1 to 10.

f. Wrap each strip in one of the supplied coloured tissue then slide it into a U-shaped holder (refer to video for visual instructions on how to wrap the strips).

g. Place the U-shaped holders in a vacuum chamber and apply a vacuum of 20 ± 5 kPa (absolute). Hold at 20 ± 5 kPa (absolute) for 20 minutes and release the vacuum.

*Note:* if your laboratory is close to sea level, then 20 ± 5 kPa absolute is about -80 kPa gauge.

h. Remove the strips from the U-shaped holders one by one and check each tissue for stain marks.

- Using a fine pen, mark the perimeter of each stain on the tissue.
- Re-wrap the strip with the same tissue in the same place as before. Use the folds on the tissue to re-align the pack, or, if necessary, put guide marks on the tissue with a pen. Replace the strip in exactly the same orientation as it was prior.
- Record the number of leaks and their position into the spreadsheet, using the reference numbers of the strips.
ANNEX 3

Terms and abbreviations

**AQL**
Acceptable Quality Limit. The quality level that is the worst tolerable process average when a continuing series of LOTS is submitted for acceptance sampling (ISO 2859–1). N.B. Manufacturers should be consistently achieving a process average that is better than the AQL.

**Bead**
The thickened ring formed at the open end of the condom.

**Bioburden**
The population of micro-organisms on a raw material, component, product, packaging or equipment.

**CE mark**
On condom packaging, a mark certifying that the product conforms to the essential requirements of the European Medical Device Directive 93/42/EEC.

**cfu**
Colony forming units - a unit of measure of the level of microbial contamination of a product.

**Compliance testing**
A regime of testing to verify that a LOT complies with the specification.

**Condom**
Medical device that is intended to be worn on the penis during sexual activity for purposes of contraception and to prevent the spread of sexually transmitted infections. Condoms are usually made from natural rubber latex but may also be made from synthetic materials, such as polyurethane.

**Consumer pack**
A wallet or carton into which one or more foil packages are inserted for marketing purposes.

**Design Requirements**
Characteristics of the condom that are specified according to the buyer’s requirements.

**Expiry date**
The date at which the product is no longer considered acceptable for use.

**Exterior shipping carton**
The container into which a number of inner boxes are packed.

**FHI**
Family Health International.
<table>
<thead>
<tr>
<th><strong>General Requirements</strong></th>
<th>The general quality characteristics of condoms that are verified before supply commences and that are not expected to vary from LOT to LOT.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV</strong></td>
<td>Human immunodeficiency virus.</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>International Conference on Harmonization.</td>
</tr>
<tr>
<td><strong>Inner box</strong></td>
<td>A box used to contain a convenient number of condoms in packages or consumer packs. Inner boxes typically contain 100–200 condoms; where a gross (144 condoms) is used as the unit of purchase, inner boxes are usually specified to contain one gross.</td>
</tr>
<tr>
<td><strong>Inspection level</strong></td>
<td>The degree of examination of the LOT, as specified in ISO 2859–1. The higher the inspection level, the more samples will be tested and, hence, the lower the risk of faulty products reaching the end-user.</td>
</tr>
<tr>
<td><strong>IUD</strong></td>
<td>Intrauterine device.</td>
</tr>
<tr>
<td><strong>ISO</strong></td>
<td>International Organization for Standardization.</td>
</tr>
<tr>
<td><strong>Length</strong></td>
<td>The length of the condom measured from the open end to the tip, excluding any reservoir.</td>
</tr>
<tr>
<td><strong>LOT</strong></td>
<td>A quantity of condoms of a single grade, class, size and composition, manufactured under essentially the same conditions. With certain exceptions, all the condoms comprising a LOT will have identical formulation; the same dimension, colour, shape and surface texture; be manufactured on the same production line; and be vulcanized under the same conditions.</td>
</tr>
<tr>
<td><strong>LOT number or code</strong></td>
<td>A unique identifying alphanumeric code assigned to a LOT.</td>
</tr>
<tr>
<td><strong>Lowry method (modified)</strong></td>
<td>A method for determining the water-extractable protein levels in latex products.</td>
</tr>
<tr>
<td><strong>Manufacture date</strong></td>
<td>The date on which the condoms were dipped.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MSDS</td>
<td>Material Safety Data Sheet.</td>
</tr>
<tr>
<td>National Regulatory Authority</td>
<td>A regulatory body with authority in a specific country to control the importation and distribution of medical products. See also Regulatory authority.</td>
</tr>
<tr>
<td>Package</td>
<td>The foil sachet in which the condom is sealed after manufacture.</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health.</td>
</tr>
<tr>
<td>Performance Requirements</td>
<td>The critical tests of quality that all LOTS must pass in order to provide adequate consumer protection.</td>
</tr>
<tr>
<td>Prequalification</td>
<td>The steps taken by the buyer to verify a manufacturer’s suitability to provide condoms of the required quality. The WHO/UNFPA Prequalification Scheme includes periodic assessment of manufacturing dossiers, testing of samples and factory inspection.</td>
</tr>
<tr>
<td>Pre-shipment compliance testing</td>
<td>A regimen of compliance tests carried out before a shipment leaves the supplier’s factory.</td>
</tr>
<tr>
<td>Regulatory authority</td>
<td>A national or international body set up to oversee the safety, efficacy and quality of medical devices, including condoms, imported and distributed within a country or region.</td>
</tr>
<tr>
<td>Reservoir</td>
<td>A narrow portion of the condom at the closed end, designed to contain ejaculate. The reservoir is sometimes called the teat.</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>The period of time after manufacture that the product is considered acceptable for use.</td>
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<tr>
<td>Social marketing</td>
<td>The use of commercial marketing techniques to distribute, promote and sell products and services of social importance, often at a subsidized price.</td>
</tr>
<tr>
<td>Specification</td>
<td>A detailed statement of a product’s requirements as established by the buyer. Usually, a specification is based on an established standard.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Standard</td>
<td>A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory authority.</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infection.</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS.</td>
</tr>
<tr>
<td>USFDA</td>
<td>United States Food and Drug Administration.</td>
</tr>
<tr>
<td>Viscosity</td>
<td>The resistance to flow of a fluid.</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>The thickness of the latex film.</td>
</tr>
<tr>
<td>Width</td>
<td>The dimension measured 30 mm from the open end at a right angle to the length of the condom when it is unrolled and laid flat without any creases.</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization.</td>
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</tbody>
</table>
WHO/UNITED NATIONS POPULATION FUND (UNFPA)

GUIDANCE ON CONDUCTING POST MARKET SURVEILLANCE OF CONDOMS

(July 2019)

DRAFT FOR COMMENTS

Medicines Quality Assurance working documents will be sent out electronically and they will also be placed on the Medicines website for comments under “Current projects”. http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

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W HO/UNITED NATIONS POPULATION FUND (UNFPA)  
GUIDANCE ON CONDUCTING POST MARKET  
SURVEILLANCE OF CONDOMS

1. INTRODUCTION

Good quality condoms conforming to the WHO/UNFPA Technical Specification for Male Latex Condoms 2017 have excellent storage properties. The combination of individual condom packaging, inner boxes and shipping containers is designed to protect the condoms during shipping and storage. Nevertheless, storage under poor conditions and/or rough handling during shipping might adversely affect the properties of the condoms. Exposure to such adverse conditions is potentially more likely once the condoms have left control of the purchaser and are in the wider distribution chain. For this reason, periodic surveillance testing of product recovered from the field is recommended to confirm that the condoms are still fit for purpose.

Surveillance testing may have to be undertaken when there are complaints about condoms, particularly if the complaints are clustered and associated with one specific product or even a single lot of product. In such cases, sample sizes can be severely limited and it may be necessary to limit testing to just one property. The selection of sample sizes for such testing can be challenging and the results may be of limited use if only a small number of samples are available.

2. SAMPLING

In order to conduct post market surveillance testing on male latex condoms, it might be necessary to recover condoms from any of the following locations:

- warehouses;
- distribution centres;
- wholesalers;
- clinics; and
- retail outlets.
Key issues when recovering samples for surveillance testing are often the sample size and lot integrity. If single lots are being tested, for example, one lot each from a number of manufacturers, then ideally the sampling plans given in Annex B of ISO 4074 should be used. If possible, samples should be taken from at least three lots from each manufacturer to give some idea about lot to lot homogeneity. If multiple lots from a single manufacturer are being evaluated then the sampling plans of Annex A of ISO 4074 are acceptable. If sample sizes are limited then it may be necessary to test only for selected properties.

Sample only for the tests that are needed to check on the parameters in question. Obtaining sufficient samples from warehouses, distribution centres and wholesalers is not usually problematic but sampling from clinics and retail outlets often means that sample sizes have to be restricted. This may limit the types and numbers of tests that can be completed.

If sample sizes are restricted, then sample sizes should still be selected from ISO 2859-1, Sampling procedures for inspection by attributes, Part1. Specification for sampling plans indexed by acceptance quality level (AQL) for lot-by-lot inspection. Try and select sampling plans that have at least a 95% probability of acceptance if the quality of submitted lots is at the limit of the specified AQL (refer to tables X-A through to X-R of ISO 2859-1 for the operating characteristic curves and acceptance probabilities of the sampling plans). Use sample sizes that are consistent with ISO 2859-1. Do not, for example, use sample sizes that fall between the specified sample sizes in the tables (for example Table II-A). Doing so can result in situations where it is not possible to make a decision about whether or not the product sampled conforms to the specification. If there are insufficient samples available to use a specified sample size then go down to the next lowest specified sample size for which there are enough samples.

For performance requirements, such as burst properties, freedom from holes and package integrity, try and avoid zero accept sampling plans whenever possible (for example, a sample size of 50 for an AQL of 0.25 with an acceptance number of 0). These sampling plans generally have poor operating characteristic curves which can lead to type I and type II errors (i.e. incorrect rejection of a true null hypothesis and failure to reject a false null hypothesis respectively, or more simply, false positive and false negative results). If forced due to shortage of samples to use zero accept sampling plans then be cautious about any conclusions that are reached.
At the time of sampling, full details about the lots being sampled including the lot numbers, expiry dates and storage conditions should be noted. More information about taking samples is given in Section 3, Guidelines for Procurement. Whenever possible, a sampling agency should be used and samples should be taken from lots using procedures to ensure the random selection of condoms from within the lot.

In some cases, it may be necessary to combine samples from more than one lot in order to achieve an adequate sample size for testing. This should be regarded as a last resort situation and is best avoided. Full details of the lots sampled must be recorded and note made of the expiry date for each lot sampled. If possible, samples from the different lots that are to be combined should be kept separate throughout the testing process to facilitate analysis of the final results. It may be possible, for example, to show that the different lots sampled have very similar properties and so justify using the overall result as an estimate of the quality of all of the lots sampled.

If the test laboratory is located some distance from the location at which the condoms are being sampled then consideration has to be given to the transport arrangements needed to get the condoms to the laboratory. It is essential to ensure that the condoms will be not be subjected to any adverse conditions in transit that could affect the results of the tests. Sending samples by airfreight might, for example, compromise the outcome of any testing for package integrity. The use of data loggers to monitor temperatures during shipment can be considered, particularly if the condoms are being shipped from or through countries with hot climates.

3. TESTING

The primary focus for testing natural rubber latex male condoms should be the critical performance parameters, i.e. burst properties, freedom from holes and package integrity. Other properties, such as dimensions, are unlikely to change during storage or shipping. Burst properties can be evaluated on a variables basis as well as on an attribute basis (i.e. conformance to the 1.5 AQL for burst properties). Information about average burst volume and pressure, their associated standard deviations and the frequency distributions of the results can be extremely useful in trying to determine if any significant changes have occurred. Comparisons can be made with the original manufacturer’s data and the pre-shipment test results. The statistical significance of any changes in properties can be readily assessed by the t-test or analysis of variance (ANOVA). Using such methods may be particularly informative in situations where there are insufficient samples available to make reliable estimates of conformity to the AQLs on an attribute basis.
4. SELECTION OF LABORATORIES

Laboratories used for surveillance testing shall be accredited to ISO 17025 for the tests being carried out. The laboratories should also participate in an appropriate international inter-laboratory proficiency scheme. Ideally, the same laboratory that did the original pre-shipment testing should be used. This makes the comparison of results much easier and more reliable and permits samples that have been retained under controlled conditions by the test laboratory to be retested if necessary.

For more information about the selection of laboratories refer to the document “Condom Quality Assurance”

Consideration should also be given when selecting test laboratories to any local customs and import restrictions. Some countries have restrictions on the import of condoms without testing and these rules can even be applied to samples being imported solely for test purposes. Check with the laboratories concerned to make certain that all rules relating to the import of products for testing are followed.

5. INTERPRETATION OF RESULTS

Although lot conformity is assessed on an attribute basis, the use of means and standard deviations whenever possible is recommended. This primarily applies to burst testing. Trends in burst properties, particularly when compared to the results from pre-shipment testing, can provide early warning of potential problems.

Reviewing the burst result histograms can reveal very interesting information. Bimodal (or even poly-modal) distributions of burst pressure and/or volume are indicators of poor within lot homogeneity. In some cases, this might indicate that the product is counterfeit, the lot in question consisting of mixed condoms from different lots or even condoms from different manufacturers. If counterfeit product is suspected then forward all of the details to the manufacturer whose name is marked on the pack. The manufacturer should be able to determine the authenticity of the product from the lot number. Counterfeiters commonly make small mistakes with labelling so return samples of the packaging and any information received with the product to the manufacturer for checking.
If regular post market surveillance testing is being carried out on products from a specific manufacturer then analysis of trends over time can provide extremely useful information. Plotting charts, as described in the document “Condom Quality Assurance – Annex 2”, for example, is a very powerful method of identifying any concerning trends in product quality. Early identification of an unacceptable trend might, for example, permit a manufacturer to carry out corrective and preventative actions before the product goes out of specification and lots are rejected. Charts can also be used to identify situations where manufacturers may have made changes to the product or production processes and failed to inform the purchaser. Comparing trends for pre-shipment test results with those from surveillance testing might also identify problems relating to the shipping and storage of a product.

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WHO/UNITED NATIONS POPULATION FUND (UNFPA)
RECOMMENDATIONS FOR CONDOM STORAGE
AND SHIPPING TEMPERATURES

(July 2019)

DRAFT FOR COMMENTS

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WHO/UNITED NATIONS POPULATION FUND (UNFPA)  
RECOMMENDATIONS FOR CONDOM STORAGE  
AND SHIPPING TEMPERATURES

1. **DURING SHIPMENT**

Store condoms in dry conditions away from direct sources of heat and sunlight.

The average mean kinetic temperature\(^1\) during shipment should not exceed 30 °C. Peak temperatures should not exceed 50 °C\(^2\). The use of data loggers to monitor all shipments that originate, terminate or transit hot climatic zones is recommended.

2. **WAREHOUSE STORAGE**

Store in well ventilated, dry conditions away from direct sources of heat including sunlight.

Long-term average storage temperature should be less than 30 °C. Short-term temperature excursions should not exceed 40 °C.

Condom factories prequalified by UNFPA will have provided evidence to verify the claimed shelf-life of the product. The shelf-life is determined by a real-time study, conducted at a specific temperature (30 °C ±5/°C) because this is the mean kinetic temperature of the most extreme climate in climatic zones III and IV. Research has demonstrated that properly packaged good-quality condoms stored at average temperatures in tropical climates do not deteriorate during storage. More information about the recommendations for storage and shipment, and the rationale for choosing 30 °C ±5/°C as the storage temperature for stability studies, is given in the Technical Basis Paper of the WHO/UNFPA Technical Specification for Male Latex Condoms.

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\(^1\) Temperatures during shipping can be monitored using data loggers. Most modern data loggers can automatically calculate and printout the mean kinetic temperature (in some cases, data has to be downloaded and analysed using provided software).

\(^2\) Brief, short term temperature excursions up to 50°C have limited impact on mean kinetic temperatures.
Since the shelf-life of the condoms will have been determined at 30 \( +5/-2 \) °C, air-conditioned storage is not necessary but it would be an advantage in hot climates, if available. In hot climates, it is important that condoms are stored in a well-ventilated environment away from direct sunlight and other sources of heat in order to minimize the exposure of the condoms to high temperatures. Similar precautions should be taken during transportation and delivery. In general, the storage temperature should be as low as can practically be achieved. Condoms stored outdoors in shipping containers are particularly vulnerable as the temperatures inside containers can be substantially above ambient temperatures resulting in faster deterioration.

Storage time in containers should be minimized. The condoms are sealed in individual foil packages, which are themselves packed in cardboard. The cardboard storage containers are vulnerable to moisture and should be stored in a dry storeroom away from walls and placed on pallets to protect against rising damp. Ideally, cartons should be stored at least 10 cm off the floor, 30 cm away from the walls and stacked no more than 2.4 metres high.

Condoms are fully protected by the individual foil package. However, cosmetic damage to the foil and damage to the outer packaging can make the product appear damaged and therefore less acceptable to the user. Contaminants of any sort (e.g. powders or liquids) should be avoided.

Condoms should be left in their original cartons and inner boxes until needed for distribution. The cartons should be positioned so that the lot number and expiry date are visible. The cartons should be identified and their locations recorded to ensure that specific lots can be located. Lots should be released on a first expiry—first out basis (FEFO).

Damaged or expired condoms should be kept separately and clearly segregated. Disposal of such condoms should be in accordance with local procedures for the disposal of damaged medical devices.

WHO/UNITED NATIONS POPULATION FUND (UNFPA)

GUIDANCE ON TESTING OF MALE LATEX CONDOMS

(July 2019)

DRAFT FOR COMMENTS

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If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.
1. INTRODUCTION

Condoms are tested as per the WHO/UNFPA specification by independent laboratories. These laboratories have to be accredited to ISO 17025 for the test methods in ISO 4074 in order to be considered for testing services. The following guidance has been developed to assist the laboratories to standardize testing and reduce variability. The guidance is meant to supplement the specific ISO 4074 tests.

2. DETERMINATION OF LENGTH (ISO 4074:2015, ANNEX D)

- Condom length can be measured directly, using a suitable calibrated mandrel, or automatically, using one of the instrumented machines now available.

- The automatic methods have the advantage that data can usually be transferred directly to any computerised record system, although it is important that the equipment is validated and regularly calibrated following the methods recommended by the manufacturer.

- A standard mandrel (described in ISO 4074) is used to normalise the measurements, as different condom designs can have different shapes at the teat and closed end.

- As a rolled condom can retain a memory of the roll when unrolled, it is permitted to stretch the condom a little (no more than 20 mm, and no more than twice) when unrolled to help remove any wrinkles persisting after the unrolling.

- Condoms can be measured lubricated but handling a lubricated condom can be difficult as the lubricant can cause the condom to stick to itself in pleats or creases. A lubricated condom may also not hang freely over the mandrel and, if stretched, can be held in the extended state by the lubricant. The condom can be powdered to ease the handling problems, as described in the standard, with or without removal of the lubricant.

- Owing to the way the bead is formed, the condom length may not be exactly the same at points around the condom. It is important to measure the length at several points and record the minimum. The instrumental methods may do this automatically.
When measuring the length manually, it is important that the measurement is taken with the bead of the condom at eye level to avoid any parallax errors. It may be easier to position the mandrel on a stand to bring it up to the eye level of the operator. Again, the instrumented methods will take this into account.

Note that the condom length should be measured to the nearest 1 mm.

3. **DETERMINATION OF WIDTH (ISO 4074:2015, ANNEX E)**

Condom width can be measured directly, using a ruler, or automatically using one of the automated machines now available.

The automatic methods have the advantage that data can usually be transferred directly to any computerised record system, although it is important that the equipment is validated and regularly calibrated following the methods recommended by the manufacturer.

When measuring directly, using a ruler calibrated in mm, it is important that the condom is positioned so that the axis of the condom is exactly perpendicular to the ruler.

Note that the end of a ruler can get worn and the corners rounded so it is better to position the condom to use another point, (e.g. the 10, 20 or 100 mm index) as the zero. The condom should be measured at the narrowest point within the range 20 to 50 mm from the open end.

Condoms can be measured lubricated but handling a lubricated condom can be difficult as the lubricant can cause the condom to stick to itself in pleats or creases. Gently manipulate the condom to smooth out any such creases, ensuring that the condom is not stretched as sometimes the lubricant can hold the condom in an extended state. It may be better to remove the lubricant and lightly powder the condom, especially if the same condoms will be used for the determination of length.

Note that the condom width should be measured to the nearest 0.5 mm which will require the measurement to be interpolated if the scale is in whole mm.
4. **DETERMINATION OF THICKNESS (ISO 4074:2015, ANNEX F)**

ISO 4074 allows two methods for the measurement of thickness, one based on the direct measurement by a micrometer, and the other by mass. The mass method was introduced owing to the fact that the precision and reproducibility of the micrometer method was found to be relatively low. One of the reasons for this is to accommodate condoms where the surface is not smooth and also it is thought to be that the preload applied to the foot of the micrometer to ensure good contact with the material under test can compress the film slightly. In some cases this preload has also been found to be well outside the required range.

Any lubricant on the condom is removed by washing or wiping the condom with propan-2-ol, and removing the lubricant can make the condom difficult to handle. If any powder is added to facilitate handling and sample preparation, this must be removed before measuring.

The thickness of a condom can vary along and around the condom and, for this reason, thickness is measured at three points on the condom: the mid-point (± 5 mm) of the condom, 30 ± 5 mm from the closed end and 30 ± 5 mm from the open end. If the micrometer method is used, then three measurements, approximately equally spaced around the condom, are taken at each location and averaged. The mass method, of course, will give the average thickness of the sample being measured.

4.1 **Mass method**

The mass method calculates the volume of the sample by dividing the mass of the sample by the density of natural rubber. If the length and width of the sample are known, then the thickness can be simply calculated.

The formula, as given in Annex F of ISO 4074:2015, is:

\[
\text{Thickness (in mm.)} = \frac{1}{0.92} \times \frac{1}{A} \times m
\]

using a density of 0.92 g/cm³, and where A is the area of the test piece (length in mm. x 20) in mm² and m is the mass of the sample in mg. If the condom is not parallel-sided, then measure both of the long sides and use the average.

The method specifies the test piece for tensile testing as the sample. This has the advantage that many laboratories already have the cutting die to give a 20 mm wide ring test piece from a condom.
Whilst there will be very slight differences in the density of the condom, caused by differences in the formulations, these will not cause any significant changes in the calculated thickness.

4.2 Micrometer method

The micrometer method measures the thickness of the sample directly using a calibrated dial or digital micrometer capable of reading to the nearest 0.001 mm. If the condom is textured, then micrometer measurements on the textured portion can give false results. In this case, measure the condom at a non-textured region as close as possible to the specified points (and report this with the results). Alternatively, the mass method could be used. Zero the gauge after measuring each sample.

Because of the compressibility of rubber, it is essential that the foot pressure is within the specified 22 ± 5 kPa and the foot pressure should form part of the regular calibration procedure for the gauge. Note that powder or lubricant on the shaft of the gauge may increase friction when the gauge is used, altering the foot pressure. For this reason, it is important to ensure that the gauge is kept clean.

It is essential that the foot of the micrometer is exactly parallel to the platen. If not, then the edge of the foot, rather than the face, will contact the sample. Under the defined load, the edge can dig into the sample and give a false reading. A photograph of an incorrectly adjusted gauge is shown in figure 1. Correct alignment can be checked by measuring a slip gauge or a feeler gauge using several positions around the very edge of the foot of the micrometer (figure 2). If the micrometer is correctly set up the readings will be the same from all sides of the foot.
Consultation Documents

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Figure 1. The foot of this micrometer is incorrect and will give the wrong reading.

Figure 2. Showing the measurement positions to confirm that the foot is parallel to the platen. Note that, according to clause 5.5.12 of ISO 17025: 2005, test equipment shall “be safeguarded from adjustments which would invalidate the test result”. It is therefore recommended that parts of the gauge that can be adjusted, such as the bezel on a dial or any adjustments on the gauge mount, are made tamper-evident. A small sticky label signed by an authorized person and placed over the part is a simple way to achieve this.
5. DETERMINATION OF BURSTING VOLUME AND PRESSURE (ISO 4074:2015, ANNEX H)

The burst properties of condoms are important properties and are frequently one of the parameters that show up differences in inter-laboratory testing. There can be many reasons for testing variability of which the following are thought to be the most important.

- loading of the condom onto the mandrel;
- correct inflation length;
- slippage of the condom during inflation;
- correct calibration of pressure and volume measuring equipment; and
- any corrections for variations in atmospheric pressure owing to the altitude of the test laboratory.

Note that recommendations for calibrating the air inflation equipment are given in Annex O of ISO 4074:2015.

5.1 Loading of the condom onto the mandrel

Condoms are almost always tested lubricated and a lubricated condom can be difficult to handle. One of the problems resulting from this is that the condom may be stretched too far on loading. In this situation, especially with burst test machines that use a wide supporting mandrel, the lubricant can cause the condom to stick to the mandrel or inflation cuff, preventing the extended condom from recovering fully. As a result, the tested length of the condom is less than it should be. This will lead to a falsely low burst volume and a higher burst pressure.

The opposite situation can occur, especially if the operator is trying too hard to avoid stretching the condom! This can give a condom that is positioned too loosely on the mandrel. In this case, the tested length will be greater than specified giving burst volumes that are erroneously high and burst pressures too low.
The correct way to load the condoms is as follows:

- Remove the condom from the pack, taking care not to damage it (it is recommended that gloves or finger cots are worn).
- Whilst it is permitted to unroll the condom before loading, it will generally be much easier to unroll the condoms directly onto the supporting rod or mandrel.
- Place the rolled condom onto the top of the supporting rod or mandrel, and using the finger tips stroke the condom down, a little at a time, allowing the condom to relax for a few seconds after each stroke.
- Ensure that the condom is not stretched as it is unrolled over the supporting rod/mandrel.

5.2 Ensuring the correct inflation length

As described in 5.1 above, ensuring the correct length of the condom to be inflated is important. Assuming that the condom is loaded correctly, this length will be dictated by the length of the supporting rod or mandrel. This will generally be adjustable and can be checked using the following method or one recommended by the equipment manufacturer:

- Load the condom onto the test machine.
- Clamp the condom.
- Mark the condom, using a suitable pen or marker, as closely as possible to the top of the external clamping collar. Depending on the type of burst test machine, clamping the condom will also start the inflation. In this case, the inflation needs to be stopped as soon as possible so the condom can be marked, or the condom marked as soon as possible and the test aborted so that the condom is not inflated and burst.
- Measure the length of the condom to the mark using the condom length measuring mandrel described in Annex D of ISO 4074. The length to the mark should be 150 ± 3 mm.
- If the tested length is outside of these limits, adjust the machine and repeat the measurement to confirm that the tested length is correct.
- Repeat for each inflation head on the test equipment.
5.3 Checking that the condom does not slip during inflation

Most air inflation equipment clamps the condom by inflating an elastic cuff against a rigid collar, clamping the condom in between.

Obviously, no matter how carefully the condom has been loaded onto the test equipment, if it is not firmly held by this clamping mechanism and the condom slips during the test, then errors will be introduced into the results. The effectiveness of the clamping system can be checked in a similar fashion to the inflation length described in 5.2 above. In this case, after marking the condom, allow it to inflate whilst watching the mark. Any slippage in the clamping mechanism will be shown by the mark moving upwards (usually erratically) as the condom inflates. It is also important to check that these cuffs do not leak, as any unmonitored air entering the condom will give false results. This can be checked by inflating the cuff, turning off the air supply (if the machinery will allow this) and checking that the cuff remains inflated over a period of several minutes.

Again, check all the inflation heads on the test equipment.

5.4 Calibrating the volume and pressure measuring equipment

Owing to the different types of condom burst equipment used in the industry, no recommendations on the calibration and verification procedures can be made here, other than to calibrate the machines following the manufacturer’s instructions. The calibration interval again can be specified by the manufacturer, and will typically be between one and four times a year, although if the equipment is subject to heavy use it may be worth calibrating more frequently. If there are any reasons to suspect that the results from a particular machine or test head are not accurate, then investigation and re-calibration should be undertaken immediately.

5.5 Correcting for variations in atmospheric pressure owing to the altitude of the test laboratory

The calibration procedure for inflation test machines will often require the average atmospheric pressure to be entered. It is important that this is adjusted accordingly, especially for test laboratories situated at high altitudes. More detailed instructions will usually be found in the manufacturer’s support literature or can be sought directly from the manufacturer.
5.6 Other factors to consider in the burst testing of condoms

- Ensure that the flow rate is within the specified range of 24-30 dm$^3$/min.

- When a condom is inflated, there is a region of high stress between the part of the condom that is firmly clamped and the adjacent freely expanding part. Owing to the characteristics of latex dipping, this zone is also usually the thinnest. Care must be taken to remove any potential for damage in this area. ISO 4074 specifies that the edge of the rigid collar is rounded with no sharp edges but this edge should be checked regularly to ensure that it has not been nicked or damaged and is still adequately smooth.

- Inflation testing machines can test a lot of condoms between service intervals and in general these condoms will be lubricated. It is not uncommon for lubricant to build up in the various holes supplying air to the condom or the piping connecting the condom to the pressure transducer. Not only can this lubricant build-up affect the accuracy of the test procedures but contamination of the pressure transducer by lubricant can mean an expensive replacement. Powder and fragments of rubber can also partially or completely block these apertures. It is recommended that there is a daily inspection and cleaning of these apertures, and that the piping to the transducer is inspected and cleaned regularly.

- Be aware of the possibility that the test heads in a multi-headed inflation test machine can differ. Monitor the individual heads and, if any of them appear to be giving consistently different results to the others investigate, and rectify if necessary.

- Consider storing a batch of control condoms and testing a few of them, depending on the number of test heads on the machine, every day before starting to use the inflation equipment. If the results from these control condoms are within the expected trend, that gives an assurance that the equipment is working properly. It can also be useful in detecting and quantifying any differences between operators. Graphing the results on, say, a mean and range chart will help identify if any significant changes occur.
6. DETERMINATION OF STABILITY AND SHELF-LIFE  
(ISO 4074:2015, ANNEXES K AND L)

It is a requirement of ISO 4074:2015 that the condoms should comply with the key physical property requirements (that is burst volume and pressure, freedom from holes and package integrity) throughout their claimed shelf-life. The shelf-life can only be established by a real-time study carried out at 30° C (+5, -2° C). However, a provisional shelf-life can be claimed whilst the real-time study is in progress, provided that satisfactory data from accelerated aging studies are available to support the claim. A full description of the requirements for real-time and accelerated aging stability studies is given in Annexes K and L of ISO 4074:2015.

Points to note when conducting these aging studies are:

- The condoms used in the studies must comply with the requirements of ISO 4074. The studies can only be done with condoms that have been stored in bulk for the maximum period of time specified by the manufacturer between dipping and packaging in individual sealed containers. This period shall not exceed 2 years.
- Minimum stability requirements (clause 11.2) must be established.
- Three different lots of condoms must be used in the studies.
- Select and condition sufficient extra condoms to cover some repeat testing if necessary.
- Ensure that there are contingency arrangements in place in case of equipment breakdown or power failures. You do not want to have to start the studies again from scratch.
- Ensure that the calibration and measurement of temperature are monitored correctly and the trends are reviewed to pick up early warning signals for initiating appropriate corrective and preventive actions.
- Ensure that the system of recording temperature and raising alerts in case of outages in temperature conditions are in good state of repair throughout the long period of stability studies and the alert signals are responded to immediately.
- The claimed shelf-life cannot exceed five years from the date of manufacture.
- The date of manufacture can be either the date of dipping or the date the condoms were sealed in their individual containers. Note that the labelled date of manufacture cannot be more than two years from the date of dipping.
Monitor the physical properties of the condoms at intervals during the real-time study. Two methods are described in clause K.2.4 of the standard. These are:

- Measure the airburst properties of a sample of 125 condoms from each lot and compare against the requirements of the standard, using the AQL of 1.5 (accept on 5 failures or fewer, reject on 6 or more). If one of the three lots of condoms fails, the study can continue but must be stopped if more than one set of samples fails.

- Alternatively, measure the airburst properties of a set of 32 condoms from each lot. Calculate the standard deviation (or 95% confidence interval) for burst volume and pressure. If the mean value, minus three times the standard deviation, approaches the minimum limits defined in the standard (as described in the note to clause K.2.4), this can indicate that the condoms will not pass the requirements of the standard if the study is continued and the stability study should be terminated.

If the manufacturer has condoms where the shelf-life has been confirmed by a real-time study, then these condoms can be used as controls in an accelerated aging study of a new or modified condom, as described in clause L.3.

If there are no condoms to act as controls in this way, then the provisional shelf-life must be estimated following the procedures in clause L.2.

Existing condoms whose shelf lives were established following the procedures of earlier versions of ISO 4074 (i.e. 2002 and 2014) can be considered to be compliant.

If any significant changes are made to the condom formulation, manufacturing procedures or packaging, then the shelf-life will need to be re-confirmed. A significant change, as explained in ISO 16038, is one that can be regarded as having the potential to affect performance adversely. If a change is deemed by the manufacturer not to require confirmation of shelf-life, it is strongly recommended that the reasons for this decision and all supporting test data are written up and filed.
7. FREEDOM FROM HOLES

7.1 ISO 4074:2015, Annex M

The ISO 4074 standard has two methods for performing the test for holes. The volume of water dispensed is dependent upon the average length and average width (taken at 75±5 mm from the closed end excluding the reservoir tip) of 13 condoms as described in the standard.

A. The Water Leak Test (Hang and Roll)

A suspended condom is filled with a specified volume of water and examined for visible water leakage through its walls. In the absence of any leakage, the condom is then rolled on coloured absorbent paper which is subsequently examined for signs of leakage of water from the condom. The test must be carried out exactly as described in the Standard.

Points to note:

- Before testing, using calibrated apparatus, ensure that the volume and temperature of the water dispensed are within the specified limits for the test.
- Ensure that the condom is secured on the mount in such a way as to avoid slippage during water dispensation, especially for the condoms that need volumes of more than 300 mm.
- The condom may be tapped gently to remove air bubbles present on the inner surface of the condom.
- It is essential that the rolling is carried out correctly. The water-filled condom must be rolled for a distance sufficient to allow the whole surface of the condom to contact the paper. This distance is frequently underestimated. When training operators, it can be helpful to mark the condom to show how far the condom must be rolled. The condom must be rolled through at least two complete revolutions (but not more than ten).
- Ensure that the correct amount of pressure is applied to the condom. The hand (with fingers spread) should be maintained 25 to 35 mm above the paper.
• When testing the closed end of the condom, maintain a similar level of pressure as when rolling and do not slide the condom over the paper.

• The coloured absorbent paper should be one that makes it easy to identify the blots made by the presence of holes on the condom wall. It should also allow for the rolling of the condom body for the required revolutions as per ISO 4074. Under no circumstances shall multiple absorbent papers be joined using adhesive tape.

• The condom walls may be carefully wiped with soft absorbent cloth or paper to remove excess moisture and lubricant thus allowing for easier detection of leaks.

B. The Electrical Test

Points to note:

• The equipment shall be routinely calibrated or verified for effectiveness, and maintained as per manufacturer’s specifications. This includes routine changing of the electrolyte solution as build-up of lubricant may affect the efficacy of the test.

• The different parameters that affect the test, such as voltage, should be checked before each batch/lot test, using calibrated apparatus, for conformity to specified limits.

• Not more than 25 mm of the condom should be left unexposed to the electrolyte.

• Any leaks detected by the system should always be confirmed by the rolling method done in the Water Leak Test. Note that ISO 4074:2015 specifies the Hang and Roll method must be used - not the ASTM D3492 Hang and Squeeze method.

• Note that the condoms have to be observed during filling in order to detect any holes (see M 3.3.7 third line)
7.2 **ASTM D3492 – 15, Annex A3**

**A. The Water Leak Test (Hang and Squeeze)**

This method is very similar to the Hang and Roll method except that the condom is not rolled. Instead, pressure is applied to the condom by gently squeezing it whilst it is hanging, full of water, on the test equipment. The test must be carried out exactly as described in the Standard.

Points to note when using this method are:

- After filling with water, the body of the condom should be tapped gently to dispel any air bubbles present on the inner surface of the condom.

- Do not apply too much pressure by squeezing too hard. The correct amount of distension of the filled condom is shown in figures A3.3 to A3.5 in the Standard.

- When checking the body of the condom, gently rotate the condom so that the entire surface is inspected.

- When examining the condoms for signs of leakage, ensure that any water droplets on the outside of the condom are the result of leakage and not water splashed onto the condom from any external source. If necessary, gently dry the outside of the condom with a paper towel and re-check.


This test is performed using samples which are drawn for conducting the test for Freedom from Holes and Visible Defects.

The individual sealed containers are examined by visual observation for any visibly open seal defects which include improperly formed seals, condoms getting trapped in sealing area, uneven or very narrow sealing edges leading to open seals and leakages. It is recommended that the test laboratory has the display of defects related to visibly open seals to serve as examples of workmanship criteria so that consistency is maintained in conducting the test. The defectives observed should be preserved for reference.

The test for visible defects is conducted on the same set of samples taken for the test for Freedom from Holes.

After performing the test for visibly open seals, the individual sealed containers are opened by pushing the condoms to one side of pack and opening the seals, taking care that the condom is not damaged by the rough edges of the seals, nor sharp instruments such as scissors or finger nails. The condoms are unrolled and examined by visual observation under bright light. It should be ensured that all the parts of the condoms are completely covered by the visual observation. The visual defects are classified as Critical and Noncritical defects with corresponding AQLs of 0.4 and 2.5. The section on Workmanship and Visible Defects on the WHO/UNFPA Specification details the list of Critical and Noncritical defects. This section also lists the minor imperfections, which do not affect the properties of the condoms, but are considered as potential points for elimination with appropriate quality improvement projects. Personnel should be trained for the ability to detect the visible defects and to correctly classify them. Having an approved workmanship criteria album will be useful to avoid any disputes.

10. **DETERMINATION OF PACKAGE SEAL INTEGRITY (ISO 4074:2015, ANNEX N)**

The seal on the individual condom container, whether of the standard foil pack or the “butter dish” container can, at times, be compromised. This can be caused by several factors, including misaligned sealing jaws, excessive lubricant, a misaligned or poorly rolled condom being trapped in the seal, etc. In addition, the foil may contain pinholes or, if the information on the foil is stamped on, rather than ink-jet printed, the stamping may damage the foil. All in all there are many ways in which the individual condom container can contain small holes. A consequence of this is that lubricant can leak out, and if not detected, can contaminate all the other condom containers within the same pack. In addition, a compromised foil can expose the condom to oxygen which could cause premature degradation. For this reason, it is necessary to test the integrity of the packages.
There are other tests under development which may, in time, replace this method but, for the moment, the test described in Annex N of ISO 4074:2015 is the one to be used.

Points to note:

- Working with a vacuum is potentially dangerous. Eye protection should be used when carrying out this test.

- The vacuum chamber should be closable with an air tight transparent lid so that the defective packs can be easily observed during the test.

- A vacuum level of $20 \pm 5$ kPa absolute must be used. That is approximately 20% of normal atmospheric pressure at sea level. Unfortunately, some gauges will read from 0 to 100 kPa whilst others may read from 100 (or -100) to 0 kPa (see figure 3). This can be confusing. If the gauge reads from 0 to 100, the correct level of vacuum will be the figure of 20 kPa: if the gauge reads the other way, the correct vacuum level will be 80 (or -80) kPa (figure 3). In case of doubt, remember that it is the greater level of vacuum that must be used. It will typically take at least 20 seconds - often considerably longer - for a vacuum pump to evacuate the chamber to this level. Changes in the time taken to reach the desired vacuum level can be indicative of complications in the test system or an inaccurate level of vacuum being used.

- The water level should be such that the condom packages are at least 25 mm below the surface.

- The number of packages in the chamber should be restricted so that all the packages can be clearly observed.

- A dye is often used to help detect leakage into the containers and the amount used should not obscure observation of the packages.

- If a dye is used, it should be easily washable and should not leave any deposit of colour building up as that would obstruct the observation of leakages. The vacuum container and the lid should be maintained clean.

- Using a low concentration of a low foam wetting agent (for example, a non-ionic surfactant) will help wet the outer surface of the individual condom containers and reduce the possibility of bubbles caused by air clinging to the foil.
• Observe the condom packages as soon as the vacuum pump starts - do not wait until the specified vacuum level has been reached to start the observation. By that time, all the air in a defective package may have been expelled and the stream of bubbles will have ceased.

• All of the individual containers must be opened to check for the presence of water inside. This is where the dye can be helpful, to distinguish between lubricant and any water that may have entered the pack.

• Vacuum pumps working off compressed air can be a more cost-effective option than a mechanical vacuum pump.

* * *

Figure 3. A pressure gauge reading from -100 to 0 kPa. In this case, the correct vacuum level for the test would be -80 kPa (red numerals).
WHO/UNITED NATIONS POPULATION FUND (UNFPA)

SPECIFICATIONS FOR PLAIN LUBRICANTS

(July 2019)

DRAFT FOR COMMENTS

Medicines Quality Assurance working documents will be sent out electronically and they will also be placed on the Medicines website for comments under “Current projects”.

http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.
WHO/UNITED NATIONS POPULATION FUND (UNFPA)
SPECIFICATIONS FOR PLAIN LUBRICANTS

1. INTRODUCTION

The following guidelines give the specifications for procurement of additional lubricants to be used with male and female condoms in reproductive health programmes.

These guidelines have been updated following a detailed technical review conducted at the United Nations Population Fund (UNFPA) Global Consultation on Lubricants in November 2016 in Bangkok, Thailand, and a follow-up meeting, primarily with lubricant manufacturers, held in conjunction the Thirty-fourth ISO/TC 157 meeting in George Town, Penang, Malaysia in September 2017.

The Global Consultation on Personal Lubricants was convened to review the safety of personal lubricants as research has shown users may experience irritation, burning and damaging effects to vaginal and rectal tissue and to examine the ways to produce, procure and distribute safer products for all. Hosted by the UNFPA, the United States Agency for International Development (USAID), the World Health Organization (WHO), and the International Planned Parenthood Federation (IPPF), the meeting brought together more than 80 manufacturers, researchers and technical experts, sexual health advocates and educators, and international organizations that procure lubricants for governments or local organizations.

The status of the WHO/UNFPA/FHI360 Advisory Note on the use and procurement of additional lubricants for male and female condoms published in 2012 (WHO/RHR/12.33) was also reviewed at the Global Consultation. It was agreed that the majority of the recommendations made in that note are still valid and are incorporated in this Specification. The recommendation that polyquaternary compounds should be avoided was found to be no longer supportable and has not been included in this specification.
2. **DESIGN REQUIREMENTS**

These shall be verified by review of product dossier.

<table>
<thead>
<tr>
<th>Requirements</th>
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<tbody>
<tr>
<td><strong>1. General Requirements</strong></td>
</tr>
<tr>
<td><strong>Description:</strong> Water-based lubricants shall be clear, translucent or white gels or viscous liquids. They shall be free from lumps and foreign matter, be non-staining and water washable. Silicone lubricants shall be clear, translucent or white gels or viscous liquids free from lumps and foreign matter, and be non-staining.</td>
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<tr>
<td><strong>Ingredients:</strong> Lubricants shall contain only ingredients that are safe for human use in contact with vaginal mucosa and skin during sexual intercourse. The ingredients shall be non-irritant, non-toxic and shall not liberate any toxic or harmful substance during storage and use.</td>
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<tr>
<td>Lubricants shall be free from added fragrance, colour, spermicides, herbal ingredients and special ingredients which claim specific pleasure enhancing properties.</td>
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<tr>
<td>Silicone lubricants shall contain a minimum of 30% polydimethylsiloxane (dimethicone) with a viscosity of 5 cps and above (mixtures of polydimethylsiloxanes with different viscosities are permitted).</td>
</tr>
<tr>
<td><strong>Compatibility with condoms:</strong> Lubricant shall be compatible with male and female condoms (any exceptions shall be noted in the labelling). Testing shall be conducted according to ASTM D7661, ISO 19671:2018 Additional lubricants for male natural rubber latex condoms - - Effect on condom strength or equivalent. When testing silicone lubricants containing volatile cyclomethicone, the conditioning of the condoms in the presence of the lubricants should be done under occlusive conditions to prevent evaporative loss of the cyclomethicone.</td>
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</tbody>
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### Preservatives:
Water-based lubricants shall be preserved against microbial contamination and shall contain suitable preservatives. The lubricant shall be manufactured under suitable conditions to maintain control of bioburden.

### Sterility:
Lubricants may be supplied sterile in unit dose containers.

### Manufacturer:
Lubricant shall be manufactured in accordance with certified Quality Management Systems (QMS) and in compliance with national and regional regulatory requirements. The QMS shall comply with ISO 13485. Lubricant shall have regulatory approval such as CE Mark or US FDA 510(k).

### Lubricity:
There are currently no specification requirements for lubricity, nor are there any recommended methods for measuring lubricity. Manufacturers who specify lubricity requirements should submit details of the specification and test method to UNFPA. Similarly, manufacturers who test for the retention of lubricity over time of use should submit details of the test method and requirement.

## 2. Composition
The manufacturer shall submit to procurement agencies full composition details of lubricant with quantities and specifications of individual ingredients used. Wherever available, the ingredients shall comply with corresponding pharmacopoeia specifications. When specific proprietary ingredients are used, their material safety information shall be submitted.

Water-based lubricants shall be formulated to comply with following requirements:

a) Osmolality shall be less than 1200 mOsm/kg\(^9\).
   
   This osmolality limit can be achieved by keeping the total glycol content below about 8.3 mass fraction (%w/w)\(^10\).

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\(^9\) This requirement is under review and might be revised at a future date.

\(^10\) This limit may be varied depending on the specific glycols used.
b) pH shall be in the range 5.0 to 7.0\textsuperscript{11}.

c) Viscosity shall be within the tolerance of ± 10 % of the value specified by the manufacturer. The manufacturer shall submit the method of determination of viscosity, giving details of equipment, temperature conditions, spindle speed, spindle number and shear rate.

The manufacturer shall submit to the procurement agency full composition details of the lubricant with quantities and specifications of individual ingredients used. Wherever available, the ingredients shall comply with corresponding pharmacopoeia specifications. When specific proprietary ingredients are used, their material safety information shall be submitted.

Silicon-based lubricants shall be formulated to comply with following requirements:

a) Viscosity shall be within a tolerance of ± 10 % of the value specified by the manufacturer. The manufacturer shall submit the method of determination of viscosity, giving details of equipment, temperature conditions, spindle speed, spindle number and shear rate.

b) Lubricants shall contain a minimum of 30% polydimethylsiloxane (dimethicone) with a viscosity of 5 cps and above (mixtures of polydimethylsiloxanes with different viscosities are permitted).

3. Biocompatibility

Lubricants shall comply with requirements of biocompatibility assessments conducted in accordance with ISO 10993 – 1, for specific parameters of cytotoxicity (ISO 10993-5) and skin irritation and sensitization (ISO 10993-10)\textsuperscript{12}. The toxicity study reports shall be reviewed and interpreted by qualified toxicologist. Full reports of biocompatibility assessments shall be submitted as part of product dossier.

\textsuperscript{11} Note: lubricants with a low buffering capacity that do not disturb the pH of the vagina or rectum are preferred.

\textsuperscript{12} Note: Some regulatory authorities require acute systemic toxicity to be assessed. For example, the USFDA require acute toxicity testing by intraperitoneal administration.
4. **Bioburden levels**

Lubricants need not be sterile. However, they shall be subjected to control of microbial contamination by appropriate measures taken in formulation, manufacturing and packing operations. In the finished product, bioburden levels shall be maintained below 100 CFU per gram (USP 1111). There shall be an absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Escherichia coli*. These requirements apply to both water-based and silicone-based lubricants.

Bioburden levels shall be maintained at the above levels during storage and repeated opening of container during multiple use.

Lubricants shall comply with the Preservative Efficacy evaluation performed as per the requirements of pharmacopoeia.

If the lubricant is claimed to be sterile, it shall comply with a Sterility Assurance Level of $10^{-6}$.

5. **Shelf-life and stability**

Lubricants shall have a minimum shelf-life of three years from the date of manufacture.

To ensure compatibility with condom storage recommendations and shelf-life estimates, real time studies shall be conducted within the temperature range of 28°C to 35°C. The humidity shall be maintained at (75% ± 5%) RH to ensure conformity with Zone IVb requirements.

In line with ICH guideline Q1A(R2), accelerated studies shall be conducted at 40°C ± 2°C/75% RH ± 5% RH. Manufacturers may elect to use higher temperatures such as 50°C and 60°C providing the results can be correlated with real time shelf-life estimates at 28°C to 35°C.

For water-based lubricants, manufacturers should include freeze thaw cycling in their stability studies to confirm that the lubricants can tolerate freezing.

Critical parameters, including pH, bioburden, viscosity, odour, physical condition, etc., shall be monitored during stability studies. For water-based lubricants, preservative assays and microbiological challenge tests shall be conducted.
during stability studies. Silicone lubricants containing cyclomethicone should be monitored for weight loss due to any loss of volatile material through the packaging.

Lubricants shall remain within the manufacturer’s specification for the duration of the shelf-life period.

The data and report on accelerated stability studies and ongoing real-time studies shall be submitted as part of product dossier.

6. Compatibility with condoms

The manufacturer should submit reports of compatibility studies conducted on the use of lubricant with male and female condoms made from natural rubber latex and synthetic materials.

Any exceptions from testing or incompatibilities shall be noted.

7. Packaging

**Individual containers:**
Lubricants shall be packed in tamper evident containers facilitating multiple delivery of lubricant. Examples are collapsible/squeeze tubes and containers with a suitable delivery system for application of lubricant.

It is recommended that containers should be made of recyclable materials, compatible with lubricant as substantiated by stability studies and shelf-life claims. The containers shall not have sharp edges. The containers shall not liberate any toxic or harmful substance during storage and use of the product. The individual containers shall be free from leakage of lubricant.

The recommended nominal contents for multi-dose containers are 35g, 50g and 82g. Other sizes may be considered depending upon programme requirements. The recommended nominal contents for a single dose sachet is 3g for silicone lubricants and 4 to 5g for water-based lubricants.

Pack contents are based on the amount of lubricant that can be expressed from the pack under normal use. This will be evaluated by weighing 20 full primary containers individually and weighing them again after squeezing out their contents.
Alternatively, the weight of lubricant expressed may be determined directly by collecting it in a tared container or dish.

*Secondary packing:*  
The individual containers shall be packed in secondary distribution packages of an appropriate size as per programme requirements (e.g. 25 units per secondary pack).

Cardboard boxes shall be FSC (or equivalent) marked/certified. They shall only contain paper/cardboard. Plastic coating shall not be used.

*Shipper cartons:*  
Shipper cartons shall be FSC (or equivalent) marked/certified. They shall be made of minimum 40% recycled/post-consumer material.

The gross box should only contain paper/cardboard. Plastic coating shall not be used.

The plastic carton liner shall be made from recycled material/plastic and biodegradable plastic by 2020.

**8. Labelling**

*Individual containers:*  
Labelling requirements may be subject to local regulatory requirements. Subject to any local requirements, the individual containers shall be marked with the following details:

a) Contents (specify if it is water- or silicone-based lubricant).

b) The quantity of lubricant that can be expressed from the container in normal use.

c) If in a multi-dose container, advice on the amount of lubricant to be used.

d) Manufacturer’s name and address.

e) Batch/lot number.

f) Expiry date (in YYYY-MM format).
g) Storage conditions – store at an average temperature below 30 °C and avoid exposure to direct sunlight.

h) Warnings/special notes, if any.

i) Maximum time period in which the contents can be used after the container was first opened.

j) A list of any ingredients that may be an irritant or which could cause allergic reactions.

k) A statement that the lubricant is compatible with male and female condoms (any exceptions, such as male polyurethane condoms, shall be stated on the package).

l) A statement that lubricant is not a contraceptive and does not protect against pregnancy, sexually transmitted infections and HIV. The lubricant must be used with a condom to protect against pregnancy and sexually transmitted infections.

*Secondary packaging:*

a) Contents.

b) Quantity.

c) Manufacturer’s name and address.

d) Batch/lot number.

e) Manufacturing date and expiry date (in YYYY-MM format).

f) Storage conditions.

g) Warnings/special notes, if any.

Shipper cartons (or as per UNFPA Shipping instructions to be provided by the buyer):

a) UNFPA logo.

b) UNFPA project number.

c) UNFPA purchase order (PO) number.
d) Country of destination.

e) Contents as water-based lubricants.

f) Quantity.

g) Manufacturer’s name and address.

h) Batch/lot number.

i) Manufacturing date (in YYYY-MM format).

j) Expiry date (in YYYY-MM format).

k) Weight.

l) Volume.

m) Storage conditions text “Store in well ventilated, dry storage conditions with an average temperature of less than 30 °C away from direct sources of heat including sunlight”.

n) Warnings/special notes, if any, to be defined by the manufacturer.

o) Any special shipping instructions defined by the manufacturer.

### 2.1 Lot by lot testing requirements

The manufacturer shall submit a Certificates of Analysis for each batch/lot of lubricant supplied confirming conformance to the requirements specified in this section. This section may also be used by accredited/approved laboratories for the independent testing of lubricants.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirements</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Water-based lubricant shall be clear, translucent or white gel or viscous liquid, free from lumps and foreign matter, non-staining and water washable.</td>
<td>Visual inspection on samples weighing about 5g, drawn from five individual containers from each lot.</td>
</tr>
<tr>
<td><strong>Silicone lubricants shall be clear, translucent or white gels or viscous liquids free from lumps and foreign matter and be non-staining.</strong></td>
<td>Inspection on composite sample weighing about 10g, drawn from five individual containers.</td>
<td></td>
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<td>---</td>
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<tr>
<td><strong>pH</strong></td>
<td><strong>5.0 to 7.0</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>Shall be within tolerance of ±10 % of the specified viscosity value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The manufacturer’s method of giving equipment, temperature condition, spindle, speed, etc., shall be used. Testing is to be completed on a representative sample from each lot, either from the bulk immediately before packaging or from sufficient individual containers in order to provide an adequate sample size for the viscometer.</td>
<td></td>
</tr>
<tr>
<td><strong>Bioburden</strong></td>
<td>Bioburden levels shall be maintained below 100 CFU per gram. There shall be an absence of <em>Pseudomonas aeruginosa</em>, <em>Staphylococcus aureus</em>, <em>Candida albicans</em> and <em>Escherichia coli</em>. Sterility (if claimed) shall be to the Sterility Assurance level of $10^{-6}$.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testing as: per The International Pharmacopoeia (Ph. Int.), U.S. Pharmacopeia (USP) or European Pharmacopoeia (Ph. Eur.). Recommended testing frequency: For the first 10 production lots, every lot shall be tested. Subject to all 10 lots conforming to specification, the testing frequency may be reduced to one in every 10 lots. If a lot fails, then full testing shall be reinstated until 10 consecutive lots have passed.</td>
<td></td>
</tr>
<tr>
<td><strong>Packaging and labelling</strong></td>
<td>Shall comply with requirements of packaging and labelling as given in section I, except for material of construction. Labelling languages: English, French, Spanish.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual observation on samples of 13 containers per lot/batch.</td>
<td></td>
</tr>
</tbody>
</table>
WHO/UNITED NATIONS POPULATION FUND (UNFPA)
CONDOM QUALITY ASSURANCE

(July 2019)

DRAFT FOR COMMENTS

Medicines Quality Assurance working documents will be sent out electronically and they will also be placed on the Medicines website for comments under “Current projects”. http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en

If you have not already received our draft working documents, please send your email address (jonessi@who.int) and we will add you to our electronic mailing list.
WHO/UNITED NATIONS POPULATION FUND (UNFPA)

CONDOM QUALITY ASSURANCE

1. STANDARDS

Standards are developed and published by national and international standards bodies to establish requirements for a wide range of products and services. Standards may be generic or product-specific. Standards for medical devices, such as male latex condoms, tend to focus on essential requirements for performance, quality and safety.

Many different types of organizations and bodies participate in the development of standards. In the case of standards for medical devices, the organizations include manufacturers, national regulatory authorities, researchers, consumer groups, international agencies and testing laboratories. International standards, e.g. ISO 4074, are agreed by consensus based on balloting by national standards organizations (member bodies) that participate in their development.

National regulatory authorities establish local procedures for the regulation and control of medicinal products and medical devices. In many cases, these authorities require that a product complies with the appropriate national or international standards before it can be marketed. Compliance can be voluntary but, in many cases, governments or regulatory authorities have made compliance with an appropriate standard mandatory. In addition to specifying safety, performance and quality requirements, standards also specify test methods that can be used to verify that products conform to these requirements. These test methods may be included in the standard or specified by reference.

The principal international standards authority is the International Organization for Standardization (ISO), the worldwide federation of national standards bodies. ISO is responsible for drafting international standards based on the best available evidence and practice. ISO Technical Committee 157 (ISO/TC 157)—Non-Systemic Contraceptives and STI Barrier Prophylactics is responsible, inter alia, for developing the international standard for male latex rubber condoms, ISO 4074 Natural Latex Rubber Condoms—Requirements and Test Methods. The committee has a membership of 25 countries, with representatives drawn from a wide range of interested parties including manufacturers, test laboratories, regulatory authorities and consumer associations.
There are also many regional and national standards organisations producing standards that are widely used both locally and globally. Examples include ASTM International based in the USA and CEN, CENELEC or ETSI in Europe. It is very common for national and regional standards to be based on or equivalent to ISO standards.

The third edition of ISO 4074 was published in September 2015. This edition includes a number of very important changes, all of which are designed to make male condoms made from natural rubber latex safer and more effective. The changes include:

- The procedures for determining the shelf lives of condoms have been improved and simplified.
- A wider range of different condom sizes is permitted.
- Maximum lot size limited to 500,000.
- Requirements specified for biocompatibility assessments based on ISO 10993-1.
- Recommendations included for the monitoring and control of microbial contamination (bioburden) on finished condoms including methods for determining bioburden on condoms, advisory limits for total viable counts and a list of specific pathogens that should be absent.
- Any claims for improved efficacy or safety have to be substantiated by clinical investigation.
- Extended range of minimum airburst volumes depending on condom size.
- Minor changes to the design of the clamping collar used in the burst test.
- Changes to the electrical test for freedom from holes to improve the detection of holes in the closed end of the condom.
- Inclusion of the “hang and squeeze” test from ASTM D3492 - 16 Standard specification for rubber contraceptives (male condoms) as an alternative method for assessing freedom from holes.
- A limit set for the number of individual containers with visibly open seals.
- Recommended requirements for minimum airburst properties and freedom from holes testing introduced for condoms narrower than 45 mm and/or shorter than 160 mm.
- Amendments made to the methods for determining the shelf-life of condoms including a simplified procedure for determining the shelf-life by accelerated stability studies based on fixed ageing periods at 50 °C.
- Stability studies to include testing for freedom from holes, airburst properties and package integrity.
- Detailed procedure included for determining the thickness of a condom by the micrometre.
• An alternative method included for removing the lubricant from the condom using an aqueous surfactant solution when determining the amount of lubricant on the condom.
• Revised labelling requirements.

The World Health Organization Department of Reproductive Health and Research (WHO/RHR), UNFPA Procurement Services Branch (PSB) and other partner agencies work with ISO/TC 157 to broaden the standard to provide for situations in which economic and social circumstances dictate the need for:

• Appropriate length, width and strength of the condom in relation to effectiveness, comfort and size.
• Establishment of requirements for stability data (both real-time and accelerated) to support shelf-life claims and stated expiry dates.
• Adequate protection against harsh environmental conditions due to inadequate systems of storage and distribution.
• Appropriate packaging, labelling and information on how to use condoms.
• Appropriate design options to meet users’ needs.

The current 2015 edition of ISO 4074 can be purchased from national standards organizations or from:

International Organization for Standardization (ISO)
ISO Central Secretariat
1 chemin de la Voie-Creuse CP 56
1211 Geneva 20
Switzerland
Telephone: +41 22 749 0111
Fax: +41 22 733 3430
Email: central@iso.org

Copies of the standard can also be downloaded (for a fee) from the ISO website (http://www.iso.org) and the websites of other national standards organizations.
2. SPECIFICATIONS

A specification is a statement of the procurer’s requirements and covers all of the product attributes necessary for procurer acceptance. These include the essential general and performance requirements, as well as discretionary design requirements. A specification includes and/or references test methods used to verify the quality of a product and may demand a different level of quality than a published standard requires. WHO/UNFPA and partners have prepared a specification that is internationally accepted for the bulk procurement of male latex condoms.

The WHO/UNFPA Specification for Male Latex Condoms is based, where appropriate, upon ISO 4074 and includes specific requirements for bulk packaging for public-sector distribution. The WHO/UNFPA Specification, if used in conjunction with the Prequalification Scheme and procurement procedures, will help ensure that a quality product is manufactured, purchased and distributed to the end user.

3. WHO/UNFPA PREQUALIFICATION SCHEME

Prequalification is a procedure designed to assess the capability and capacity of a manufacturer to supply a quality product before a contract is awarded. Prequalification reduces the risk of awarding a contract to a manufacturer that is unable to meet the quality requirements defined in the WHO/UNFPA Specification. The purpose of prequalification is to ensure that the male condoms procured are safe, of good quality and efficacious. The prequalification scheme is intended to protect both the procurer and the end user.

WHO/UNFPA have established a Prequalification Scheme for male latex condoms. This scheme was developed in collaboration with the manufacturing community, international agencies, the donor community and experts. The scheme was originally harmonized with the WHO Prequalification Scheme for Essential Medicines. The draft WHO/UNFPA Male Latex Condom Prequalification Scheme was approved for publication, subject to external review by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2007. The WHO/UNFPA Prequalification Scheme was then extensively reviewed electronically by a wide spectrum of public- and private-sector experts and during three workshops, held in Bangkok, Thailand; Beijing, China; and New Delhi, India, between December 2007 and March 2008. WHO published the Prequalification Scheme in May 2008; refer to WHO Technical Report Series, No. 948, Annex 2, page 71. The guidance for the WHO/UNFPA Prequalification Scheme for male latex condoms is given in Section 2 of this document.
The scheme has now been updated based on many years of experience of operation. The update reflects the changes that have taken place in the general procedures for regulating medical devices globally, feedback from manufacturers and users of the scheme.

UNFPA maintains a list of prequalified products manufactured at a manufacturing site. This list is available on the WHO and UNFPA prequalification websites. It is strongly recommended that only prequalified manufacturers be used for the procurement of condoms for public-sector distribution.

4. REGULATORY AUTHORITIES

Condoms are classified as medical devices and, as such, are regulated by various regulatory authorities around the world. These bodies license drugs and medical devices for use in a particular country or region. In addition, some carry out or commission factory audits and product testing. They generally have the power to refuse to license manufacturers, to recall products and to close factories in the event of continued noncompliance with their regulations.

It is important for purchasers to work closely with national regulatory authorities and inform them of the procurement procedures and testing protocols that will be used to verify the quality of the condoms before they are shipped to the country. Purchasers also need to be aware of and comply with any specific local regulations or requirements.

If the regulatory authority requires in-country testing, then the local laboratory should be accredited and capable of testing to internationally recognized standards. Local laboratories that are accredited can undertake, subject to a contractual agreement with the procurer, the pre-shipment compliance-testing regime recommended in to avoid the need for further testing when the products arrive in country”.

The national regulatory authority may undertake confirmatory testing and in-market compliance testing of the product to ensure that it has not deteriorated during shipping, handling and storage. Procedures for confirmatory testing are outlined in Section 3 of this document. In such cases, national regulatory authorities should use accredited laboratories that participate in appropriate inter-laboratory proficiency trials.
Two well-established regulatory procedures for condoms are the U.S. Food and Drug Administration (USFDA) 510(k) pre-market clearance procedure and the European Union CE marking scheme.

- **USFDA 510(k) pre-market clearance**: Prior to marketing a condom in the United States of America (USA), the manufacturer must submit documentation to the USFDA and obtain a pre-market clearance (510(k)). The documentation has to demonstrate that the product is equivalent to one that is already on the market. A 510(k) pre-market clearance means that the manufacturer has submitted acceptable safety data on the product and complies with USFDA requirements for the manufacture and distribution of the product. Factory audits are conducted periodically to monitor compliance.

- **CE marking in Europe**: Condoms intended for sale or distribution within the European Union must carry the CE mark which verifies that the product meets the essential requirements of the medical device directive 93/42/EEC, as amended. Manufacturers are required to follow specific conformity assessment procedures that include submitting a technical file to a European Notified Body. Compliance with EN ISO 4074 (European designation for the standard) can be taken as evidence of compliance with some of the essential requirements of the medical device directive. Manufacturing facilities are required to have certification of ISO 13485.

Most countries have their own regulatory procedures, which should cite relevant published standards. It is always necessary to review national regulatory policy and guidelines before importing condoms into and, in some cases, exporting condoms out of a country.

### 5. QUALITY MANAGEMENT SYSTEM

A well-run condom manufacturing company will have an audited, documented and effective quality management system conforming to ISO 13485. ISO 13485 is a quality management scheme specifically designed for medical device manufacture. This standard specifies requirements for documentation, procedures and structures to be followed in all types of establishments that manufacture medical devices.

The essential components a quality management system include fully documented:

- quality objectives;
- management responsibilities;
- provision of required infrastructure;
- training procedures;
- process and quality assurance procedures;
- systematic record-keeping;
- corrective and preventative action in case of product quality problems; and
- risk management.
Factories must maintain control over all incoming raw materials and have adequate in-process testing and controls, appropriate in-process remedial procedures, adequate testing of finished products and a functional record-keeping system.

Condoms are non-sterile products but nevertheless should be free from contamination and adulteration. The products therefore need to be manufactured in a controlled environment. Periodic monitoring of the environment and the product is required to ensure that bioburden levels are maintained within acceptable limits and specified pathogens are absent.

The site must be audited and certified to ISO 13485 by an accredited certification body. In most countries, these certification organizations are private companies, although in some cases they are government agencies. To determine consistency of manufacturing, the certification schemes generally focus on the effectiveness of and compliance with the factory’s documented management system. The certifying organization should be registered with an appropriate body, such as the national standards body of the country where the manufacturer or the certifying organization is located.

6. LOTS

A lot (Batch) is a collection of condoms of the same design, colour, shape, size and formulation.

A lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing and be packed in the same type of individual container, using the same packaging materials. All condoms comprising a lot will:

- have an identical formulation;
- have the same design, dimensions, colour, shape and surface texture;
- be manufactured on the same production line;
- be vulcanized under identical conditions;
- be in the same packaging;
- have the same lubricant; and
- have the same date of expiry printed on the package.

Lot sizes over 500,000 are not permitted due to the risk that the lot may not be homogeneous. Managing such large lots, for example if there is a product recall, can also be difficult.
Manufacturers should retain samples from every lot to assist in the resolution of any disputes relating to quality. It is recommended that the retained samples be kept under approved controlled temperature conditions consistent with the manufacturer's recommended storage conditions for the duration of the shelf-life of the product.

7. LOT-BY-LOT PRE-SHIPMENT COMPLIANCE TESTING

The quality of condoms can be influenced by many different manufacturing and raw material factors. The consequences of purchasing and distributing poor-quality condoms in the public sector are severe. For these reasons, WHO/UNFPA also recommends that independent lot-by-lot pre-shipment compliance testing of the finished product be undertaken, using an appropriate sampling plan from ISO 2859–1:1999 Sampling procedures for inspection by attributes -- Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection, before the condoms are accepted for shipment to the purchaser. Manufacturers with a good track record and a sustained level of delivering quality condoms with process averages significantly below the AQL may, subject to meeting specified performance criteria, qualify for reduced inspection for burst properties and skip lot sampling for dimensions, lubricant quantity, package integrity, packaging and labelling. Purchasers can consider the option of a reduced level of lot-by-lot testing, for example using the procedures specified in ISO 2859–1:1999 for reduced inspection and ISO 2859-3:2005 Sampling procedures for inspection by attributes - Part 3: Skip-lot sampling procedures.

The methods of sampling the condoms for pre-shipment compliance testing and the relative merits of testing prior to delivery are discussed in Clause 8. Either an accredited sampling agency or the testing laboratory should take the samples. The manufacturer must not select the samples. The selection of suitable test laboratories is discussed in this document in Clause 12. It is recommended that only one set of pre-shipment compliance testing be carried out and this must be done by an accredited laboratory.

Manufacturers must satisfy themselves that individual lots meet the specification before lots are submitted for pre-shipment compliance testing.

Post-shipment testing may be performed as well depending on the country of destination of the condoms. It is recommended that this testing be performed by an accredited laboratory.
8. SAMPLING

The quality of a lot is estimated by testing a random sample of condoms from that lot. The inspection levels and AQLs are specified in ISO 4074 using sampling plans specified in ISO 2859–1 Sampling Procedures for Inspection by Attributes. These are the most widely used sampling plans for assessing attribute criteria (i.e. whether the product conforms or does not conform to the requirements detailed in the specification).

Sampling for independent testing should be done by an organization accredited for sampling, by the UN inspector during inspection or by the testing laboratory and not by the factory producing the condoms. Such sampling is required for Prequalification and Pre-shipment compliance testing.

The sampler must verify that each lot that is sampled complies with the definition of a lot, as specified in Clause 7.

Samples must be:

- taken in accordance with pre-agreed sampling procedures;
- representative of the lot of condoms;
- randomly selected (preferably based on random numbers); and
- taken by or under the personal full-time supervision of the sampler.

The sample, once taken, must be sealed and dispatched under the sampler’s supervision.

Recommended detailed sampling procedures are described in Annex 1.

At the request of the manufacturer or the procurer, a duplicate sample may be taken for use in case of disputes. The sampling agency must issue a report giving full details of the sampling process. The report shall include the sampling procedures, identification of the cases from which samples are taken and the total number of cases offered for sampling. The sampler should mark the cases from which samples are taken for procurer reference at receipt.

9. ACCEPTANCE QUALITY LIMIT (AQL)

In ISO 4074 and the WHO/UNFPA Specification, the limits for the maximum percentage of defective condoms are specified in terms of Acceptance Quality Limits (AQLs). The AQL is the maximum acceptable average percentage of nonconforming products in a continuing series of manufacturing lots offered for testing. The technical definition of an AQL is given in the glossary in Annex 3.
For important performance properties, the AQLs are set as low as practically possible. For example, the limit for freedom from holes is set at 0.25% to ensure that the end user is adequately protected. For properties that are less important and do not affect the performance of the condom, such as non-critical visible defects, slightly higher AQLs are acceptable. Conformance with the specified AQLs is assessed by testing a sample from each lot. Testing a sample can only give an estimate of the percentage of defective products in a lot. The reliability of this estimate will increase with the size of the sample. The average percentage of defective products—the process average—can be estimated by pooling the results of testing from many lots. For further details on process average, refer to Annex 2.

As discussed in the previous section, testing is conducted according to sampling plans specified in ISO 2859–1. This standard contains sets of tables giving the maximum number of nonconforming products that are allowed in a sample taken from a lot. The sampling plans are designed to give a high probability (usually greater than 95%) of a lot being accepted if the process average of defective products is equal to or less than the AQL. In the long run, therefore, the percentage of lots being rejected should not exceed 5%. If it does, then there is a risk that the manufacturer is not conforming to the relevant AQL. More information on AQLs and sampling is given in Annex 2. If you need assistance, contact the UNFPA quality assurance team at qa-team-group@unfpa.org.

10. MONITORING QUALITY

As well as reviewing the results of pre-shipment compliance testing on a lot-by-lot basis, it is recommended that purchasers monitor quality on an ongoing basis. This can be done by calculating the process averages and using control charts (e.g. Shewhart® charts). Monitoring quality using these methods provides excellent information about trends in product quality and/or early warning of potential problems. Refer to Annex 2 for details.

11. TESTING LABORATORIES

Laboratories may be:

- manufacturers’ laboratories;
- independent accredited test laboratories; and
- national regulatory laboratories.
Laboratories that test condoms for regulatory or compliance purposes need to have systems in place to ensure the reliability of their results. ISO has developed a quality management system specifically for laboratories: ISO 17025. Laboratories that comply with ISO 17025 will also operate in accordance with ISO 9001. ISO 17025 covers the essential elements of ISO 9001 as well as laboratory-specific requirements, such as technical requirements for equipment, calibration, uncertainty management and technical competence of the staff. The laboratory must conduct regular, traceable calibration of its measuring equipment, have an adequate maintenance system, and have systems in place to ensure the technical competence of their staff. Condom testing laboratories used for prequalification and pre-shipment compliance testing should be accredited to ISO 17025. The laboratories should also participate in international inter-laboratory proficiency trials and, if applicable, local inter-laboratory proficiency trials for male condom testing.

There are a number of international mutual recognition agreements among accreditation bodies, which audit each other for quality. The international umbrella body is:

International Laboratory Accreditation Cooperation (ILAC)
The ILAC Secretariat
P.O. Box 7507
Silverwater
NSW 2128
Australia

(ILAC) Delivery Address:
The ILAC Secretariat
7 Leeds Street
Rhodes
NSW 2138
Australia
Tel: +61 2 9736 8374
Fax: +61 2 9736 8373
Email: ilac@nata.com.au
http://www.ilac.org

Regional accreditation bodies that collaborate with ILAC include EA in Europe, APAC in Asia Pacific, IAAC in the Americas, AFRAC in Africa, SADCA in Southern Africa and ARAC in the Arab region.
It is recommended that all laboratories - national, independent and manufacturers - confirm their competence by participation in inter-laboratory proficiency trials for testing male condoms. In such trials, laboratories test samples of condoms supplied by the trial organizers. The results of the tests are returned to the organizers who analyse them and provide feedback to each participating laboratory. The test results are reported anonymously to all the test laboratories allowing participants the opportunity to investigate any tests in which their results disagree with those of other participants.

When assessing a testing laboratory, the following factors should be considered:

- whether the laboratory is accredited by an internationally recognized body;
- whether the laboratory participates in inter-laboratory proficiency trials; and
- the reputation of the laboratory among large-volume purchasers.

12. TESTING COSTS

Some procurers question the cost of independent lot-by-lot pre-shipment compliance testing when they deal with a supplier with whom they have experience and in whom they have developed confidence.

Some have experimented with “consignment testing”, i.e. regarding the whole shipment as a single lot. The trouble with this method is that it is unlikely that the whole shipment has been manufactured under the same conditions. The shipment is therefore unlikely to meet the definition of a lot, as described in Clause 7. Since the homogeneity of the shipment cannot be guaranteed, the statistical principles behind lot sampling and testing are likely to be compromised. Furthermore, it is difficult to detect problems that may be present in individual lots.

The use of this method increases the risk of a poor lot being accepted. Procurers who have experimented with it have found that the savings were a false economy.

13. POST-SHIPMENT TESTING AND CONFIRMATORY TESTING

In many countries, national regulatory authorities review the data and conclusions reached by the accredited independent laboratory that has been contracted by UNFPA or another procurement agent to undertake the pre-shipment compliance testing. In some countries, in contrast, the national regulatory authority may require in-country testing prior to distribution, i.e. post-shipment testing.
In this case, post-shipment testing would be considered as confirmatory testing. Where feasible, the confirmatory testing should be undertaken by the same laboratory that undertook the pre-shipment compliance testing to reduce the risk of contradictory results. Where possible, confirmatory (post-shipment) testing, if required, should replace rather than repeat pre-shipment compliance testing. These requirements should be written into the contractual agreement between the purchaser and the receiving country and/or procuring agency. The testing should be undertaken by a laboratory accredited to ISO 17025.

**If pre-shipment compliance testing and post-shipment testing are undertaken, there is a risk of contradictory results, primarily due to the sampling uncertainties associated with attribute sampling.**

On occasion, the national regulatory authority may have a valid concern regarding possible deterioration of the product during transportation. If this is the case, then confirmatory testing may be undertaken. Therefore, confirmatory testing serves better when applied as part of risk-based quality assurance system.

Local regulatory authorities are encouraged to take into account the results of pre-shipment compliance testing before reaching any conclusions about the quality of the product.

Confirmatory testing can be restricted to selected a few lots, i.e. skip lot testing, chosen at random from a shipment or consignment. If one or more of the selected lots fail to comply with the specifications, the remaining lots should be tested.

It is recommended that, when such testing is undertaken, priority be given to the critical performance parameters of airburst properties and pack integrity. The risk of statistical lot failures due to sampling error should be considered when interpreting such tests. Occasional differences in results between the pre-shipment compliance tests and the confirmatory tests must be expected. Guidance on action to take in such circumstances can be found in Section 2: Resolution of Disputes.
SECTION 2: RESOLUTION OF DISPUTES

1. INTRODUCTION

There are a number of possible causes of disputes relating to quality during a contract to supply condoms. These may involve:

- interpretation of the contract;
- payment schedules;
- delays in delivery schedules;
- completion schedules;
- independent laboratory test results;
- design issues; and
- condition of the condoms upon arrival in-country or at some time after delivery.

It is essential that the procurement contract specifies a process for the resolution of any disputes that might arise over contract or product quality issues. This chapter only deals with disputes over product quality.

2. DISPUTES OVER LABORATORY RESULTS

Disputes over product acceptance most often arise when independent testing determines that the product does not conform to the required specification or standard. It is also possible for a manufacturer to dispute a decision made by the sampling agency regarding product packaging or appearance.

In most cases, manufacturers accept the results of independent laboratories and replace lots that have been rejected. When they question the results they usually present their own test results or other evidence to suggest that the independent tests are incorrect and do not accurately represent the quality of the product tested.
3. SOURCES OF DISPUTES ARISING FROM LABORATORY TESTING

Laboratory testing is always done on a sample from the production lot. There are generally two main sources of uncertainty in test results:

- **The uncertainty arising due to sampling.** There is always an intrinsic level of uncertainty in estimating the properties of any population based on testing of a sample. This uncertainty decreases as the sample size is increased. The sampling plans specified in *ISO 4074* generally provide a 95% to 99% probability that a lot that is just within specification will be accepted. (For sampling plans with acceptance numbers of zero, the probability of acceptance can be as low as 90%.) There is therefore a small risk that lots of acceptable quality will be occasionally rejected.

- **Testing or reporting mistakes due to operator error, equipment malfunction, drifts in calibration, transcription errors and other causes.** These types of mistakes are, in principle, preventable and should be minimized by application of the quality management system and procedures outlined in *ISO 17025*. In addition, there is also the normal uncertainty associated with measurement.

There are a number of important consequences that have to be considered because of the inherent limitations in the sampling plans. These are:

- In any shipment of condoms there is always a risk that some lots will be rejected even though the process averages may be at or even below relevant AQL. This risk is most severe with sampling schemes with an accept on zero, reject on one decision rule and with process averages that approach the AQL. Manufacturers can minimize such risks by ensuring that the process averages are maintained well below the AQL. For example, by operating with process averages that are half of the relevant AQLs, manufacturers can cut the risk of rejecting lots that actually conform to freedom from holes, package seal and inflation requirements to less than 1%.

- Manufacturers and purchasing agencies should plan on the assumption that some lots, possibly up to 5% in extreme cases, will be rejected. Estimates of volume requirements and pricing should take into account the impact of possible lot failures. Again, manufacturers can keep down the percentage of lots rejected by maintaining process averages well below the relevant AQLs.

- Lots with defect levels slightly above the AQL have a high and significant chance of being accepted. Lots that significantly exceed the AQL still have a reasonable chance of being accepted. It is only when the defect levels are several times the AQL that the probability of rejection becomes very high.
As a general rule, when the level of lot failures exceeds 5% over a large number of lots, i.e. 50 or more, then doubts can be raised about the quality of the manufacturer’s production. Similarly, if the percentage of lots rejected exceeds 10% in the short term (e.g. between 5 and 50 lots), then again doubts can be raised about the quality of the products. Finally, if any two lots in a sequence of five lots are rejected, there is a significant risk that the process average may exceed the AQL; further investigations of quality should be undertaken according to the techniques described in Annex 2.

4. REVIEW OF INFORMATION

If a result is disputed, the laboratory and the manufacturer should be asked to verify basic issues, as follows:

4.1 Independent testing laboratory

- Verify that testing was performed as prescribed in the test method applicable to the order concerned;
- Verify that test equipment was in proper working order and in calibration at the time of testing;
- Check on staff performance by looking at the relevant tester’s results on other products tested at about the same time;
- Verify by checking records and any retained samples the identity of the test samples and that the normal precautions were taken not to damage the samples prior to testing; and
- Verify that the appropriate uncertainty estimates have been applied for the individual non complying condoms when deciding on the pass fail decision for marginal lots. This is to see if disputed differences can be explained by uncertainty of measurement.

If the laboratory has any doubts about any of these issues, it should re-test the products free of charge.
4.2. **Manufacturer**

- Review manufacturing and test documents for completeness and for anomalies that may indicate problems; and
- Review all the items above that the independent testing laboratory is required to verify.

When the lot concerned is part of an ongoing order and there is historical or concurrent data on at least 10 lots, the process average can be estimated by one or more of the techniques given in Annex 2. If this process average is within the AQL, it strengthens the case for a re-test. Data sets from both the test laboratory and the manufacturer should be available.

5. **DECISIONS ON RE-TESTING**

If an agreement cannot be reached between the parties and retesting is undertaken, this should be done by independent third party laboratory accredited to ISO 17025 for male latex condom testing.

Before a re-test is considered, all available data should be reviewed and discussed with the independent laboratory. If a manufacturer disputes a test result, the following issues should be considered in deciding whether to allow a re-test:

- What is the margin by which the product has failed to comply?
- Is the manufacturer’s history of production for the client a good one?
- What is the nature of the difference between the manufacturer’s and the laboratory’s test results?

In particular, if an estimate of the process average for the test concerned over the last 10 lots is available, it should be taken into account.
The amount of information available for review depends on the type of test. With inflation testing, for example, data on the number of non-compliers will be available as well as the individual volumes and pressures. In this case, a detailed comparison of the data from the manufacturer and the test laboratory can be conducted and it may be possible to identify the cause of disagreement. If, however, the dispute relates to freedom from holes, then the manufacturer must provide detailed and credible pre-release and in-process test results to support the claim for a re-test. In general, a manufacturer requesting a re-test should be prepared to make in-process test data for the lot concerned available for review. Re-testing should be undertaken only when:

1. **There is considerable evidence that the laboratory has made a mistake.**

Examples of considerable evidence could be failure to produce evidence that the equipment had been calibrated properly, lack of training records and proficiency test results for the technicians conducting the tests, failure of a critical piece of equipment, evidence of data tampering, loss or mistakes, results completely out of line with other lots manufactured and/or tested at the same time, etc.

Or:

2. **There is considerable evidence that the test result is not representative of the population from which the lot sample is taken.**

The evidence for a retest in most cases will be the results for similar lots made at the same time on the same equipment.

Therefore, re-testing should be undertaken only when there is strong evidence that an error has been made. More information on the statistical issues associated with sampling is given in Annex 2.

Before a re-test is considered, all available data should be reviewed and discussed with the independent laboratory. If a manufacturer disputes a test result, the following issues should be considered in deciding whether to allow a re-test:

- What is the margin by which the product has failed to comply?
- Is the manufacturer’s history of production for the client a good one?
- What is the nature of the difference between the manufacturer’s and the laboratory’s test results?
The amount of information available for review depends on the type of test. With inflation testing, for example, data on the number of non-compliers will be available as well as the individual volumes and pressures. In this case, a detailed comparison of the data from the manufacturer and the test laboratory can be conducted and it may be possible to identify the cause of disagreement. If, however, the dispute relates to freedom from holes, then the manufacturer must provide detailed and credible pre-release and in-process test results to support the claim for a re-test.

When a lot is rejected, in case there is a dispute over a lot or shipment of condoms, then the laboratory should keep the non-conforming condoms in respect to freedom from holes, visible defects and dimensions until the results have been accepted or until the dispute is resolved.

When the lot concerned is part of an ongoing order and there is historical or concurrent data on at least 10 lots, the process average can be estimated by one or more of the techniques given in Annex 2. If this process average is within the AQL, a re-test may be allowed.

6. RE-TESTING

Where re-testing is done, the second test should give additional confidence about the result, compared with the first test. Re-testing may be done using the next higher inspection level defined in ISO 2859-1 than the one used for the first sample (e.g. G-II instead of G-I).

Because of the operating characteristics of the sampling plans specified in ISO 4074, which are primarily intended for the routine testing of a continuing series of lots, there can be a significant probability that a rejected lot will be accepted on re-test even if the lot does not conform to the relevant AQLs. This means that, in many cases, re-testing will lead to conflicting results. Therefore, re-testing should be undertaken only when there is strong evidence that an error has been made. More information on the statistical issues associated with sampling is given in Annex 2.

Where possible, the re-tested sample should be taken from the laboratory’s retained sample taken at the time of sampling. If this is insufficient, or if the sample is suspect, a new sample will need to be taken.

If disputes cannot be resolved, it is recommended that retesting be undertaken by independent third laboratory accredited for male latex condom testing.
Annex 1

Sampling Procedures for Condoms

1. ACRONYMS

EOI: Expression of Interest
ISO: International Organization for Standardization
PSB: Procurement Services Branch
QA: Quality Assurance
SO: Super Office
SOP: Standard Operating Procedure
UNFPA: United Nations Population Fund

2. DEFINITION

This Standard Operating Procedure (SOP) describes the process to be followed when sampling consignments of male condoms and female condoms.

3. PURPOSE

The purpose of this SOP is to provide guidance for the process to be followed when preparing for sampling; and sampling of male and female condoms.

4. SCOPE AND APPLICABILITY

This SOP is intended to be used by inspecting and sampling agencies, as designated by the United Nations Population Fund (UNFPA) and UNFPA/World Health Organization (WHO) prequalification inspections, and for the QA of MC/FC procurement.
5. PROCESS

The required number of individual condoms for the sample is taken in whole bulk (inner) boxes, each of which typically contains 144 or 100 condoms. The number of boxes required should be calculated based on the sample size required and the number of condoms in the bulk boxes. The individual boxes should not be opened. If any are opened, for example to confirm the number of condoms in a box, they should be resealed under the supervision of the inspector or sampling agent.

a. Determine the number of pallets in each batch of the consignment.

b. Calculate how many exterior cartons are to be checked visually, as specified in the summary of the requirements of Lot-by-Lot pre-shipment testing. The pallets that the exterior cartons are in should also be checked visually.

c. Check the condition and integrity of the outer packing material and the pallets. Amongst the verification of the conditions, the sampler (inspector) should document via a written statement, as well as photographic evidence, the conditions and integrity of the outer packaging.

d. Check the general cleanliness of the outside of the goods on the pallets.

e. Check that the overall labelling of the pallets matches the packing list.

f. Record any defects. The record should include a written statement as well as photographic evidence of the defects.

g. Count the total number of transport packs (cartons) on the pallets and verify the total against the packing list. Record the total on the inspection report.

h. Calculate the number of cartons to be sampled using the formula \( n = \sqrt{N} + 1 \), where \( n \) is the number of cartons to be sampled and \( N \) is the total number of cartons.

   i. Round up \( n \) to a whole number if necessary.

   ii. If \( N \) is less than, say, 15, then sample all of the cartons.

   iii. Sample the \( N \) cartons, using a random sampling plan, as described below, and place the samples in a separate container.
i. Randomly select the cartons to be sampled from each pallet, using one of the two methods below:

i. Option 1. Obtain the total number of cartons in the consignment from the manufacturer in advance and select the cartons to be sampled using a random number generator (e.g. by computer software or on a smartphone) or random number tables. To maintain independence, DO NOT inform the manufacturer about the actual cartons to be sampled.

ii. Option 2. Draw the samples equally (as far as possible) from each pallet. For example, if there are ten cartons to be sampled from three pallets, sample three cartons from two of the pallets and four cartons from the remaining pallet. Cartons should be randomly selected from the top, middle and bottom of the pallets, for example as shown in figure 1.

iii. Take pictures of the pallets/lots before retrieving sample boxes so UNFPA can see the total quantities available for sample dispatch.

iv. Take individual pictures of each pallet so UNFPA can monitor how the selection of boxes within the different pallets has been performed.

v. Record the number of cartons sampled and the carton number from which the samples were drawn.

j. Check the condition of the cartons for the integrity of the packing material.
k. Check the cartons for cleanliness.

l. Confirm the labels on the cartons are undamaged.

m. Confirm that the cartons are undamaged.

n. Check the labels for spelling mistakes.

o. Confirm that the expiry date is present and legible (and the date of manufacture, if required). Products should be recently manufactured and, unless specifically authorized in writing, have at least 75% of the shelf-life remaining at the time of the delivery to country of destination.

p. Check and verify the requirements in the inspection templates (Annex II and/or Annex III).

q. Record any defects and discrepancies. (Include the Lot number and Carton number of where the defect was found.)

r. Numbers of condoms to be selected from the sampled cartons. The condoms shall be selected in their bulk pack – usually as boxes of 1 gross (144 units) but occasionally as boxes of 100 units. **Note:** Samples should be taken, taking into account the actual Lot size, irrespective of pieces ordered.

   i. Standard pre-shipment testing for male condoms (no oven conditioning required). See table 1.
   
   ii. Exceptional pre-shipment testing for male condoms – oven conditioning required. See table 2.
   
   iii. Female condoms (note that female condoms are not usually packed in boxes of 1 gross). See table 3.
   
   iv. Sample the condoms based on the Lot size, not the order quantities.
   
   v. Take the condom boxes from the cartons selected for sampling. Randomly select the boxes from the top, middle and bottom of the cartons and spread the sampling across the cartons as evenly as possible.

s. Check the condom boxes for integrity of the packing material.

t. Check the condom boxes for cleanliness.
u. Check the condom boxes for distortion or discolouration.

v. Confirm that the labelling of the condom boxes is undamaged.

w. Check if there is any special artwork that may have been proposed from the country of destination is appropriately added.

x. Check the condom boxes for overall damage.

y. Check the labelling on the condom boxes for spelling mistakes.

z. Confirm that the labels on the condom boxes carry the name of the manufacturer, expiry date and date of manufacture (if required).

aa. Check the instructions for use.

bb. Record the defects. (Include the Lot number and Carton number of where the defect was found.)

6. REPORTING RESULTS

a. A summary of the inspection should be included in the report.

b. In addition to the standard content of the report, the report should include the following:

   i. Full details of goods and packaging;
   ii. Total number of cartons opened for collection of the samples;
   iii. Serial number of the cartons opened;
   iv. Number of grosses sampled per carton;
   v. Record all Lot/Batch numbers sampled;
   vi. Number of grosses per batch sampled;
   vii. Description of sealing procedure: describe how the samples were sealed in a tamper proof manner (for example, box was taped and dated).
   viii. Seal numbers, if applicable.

References

ISO 4074:2015 Natural rubber latex male condoms – Requirements and test methods.


Female Condom: Generic Specification, Procurement and Guidelines for Procurement 2012.
Annex 2

Methods for Assessing Quality of Suppliers

There are a number of methods for assessing the quality of manufacturers. Because of the uncertainty in estimating the quality of a LOT by testing a sample, as discussed in Section 1, Chapters 1 and 4, it is only by monitoring quality across many LOTS that a reliable picture can be established about the quality of a specific manufacturer. Decisions based on information from a small number of LOTS—for example, in the case of short-term or small-volume contracts—can be misleading when considered in isolation. In general, it is most important to monitor the performance related to the Performance Requirements.

Based on an analysis of data from a number of manufacturers, individual lot average values should not vary by more than ± 20% from the overall average across all lots tested. Any lot exhibiting a shift from the overall mean that is larger than 20% should be rejected, and any long-term shift in the lot averages should be investigated. Monitoring is best achieved by using a control chart (e.g. a Shewhart chart).

Unless there is specific concern about an individual supplier’s ability to comply with the design-related requirements, it is probably not worth monitoring these properties.

The methods that can be used to monitor quality are as follows.

1. **PROCESS AVERAGE**

The process average is the percentage of condoms that are non-conforming over a defined time period or quantity of production. It is calculated for each requirement detailed in the WHO/UNFPA Specification by dividing the number of non-conforming condoms by the total number of condoms tested. Ideally, the process average for a specific attribute should be not greater than half the specified AQL.

2. **CONTROL CHARTS (SHEWHART CHART)**

Control charts provide a very convenient and simple way of monitoring quality over time and observing trends in process averages. They can provide early warning of any change in quality, alerting both manufacturers and purchasers to potential problems. They can be used retrospectively to assess how stable a process is. They provide a means of correlating changes in process average with process operating conditions or change in raw material batch. Their use is strongly recommended to confirm that a manufacturer has production under control and is capable of achieving the quality levels specified.
To construct a control chart, the percentage defects for each LOT is plotted against LOT number or any other appropriate parameter such as date of manufacture.

Control charts can also be constructed for variable data, such as average burst volumes and burst pressures, and for standard deviations. Warning and control limits are usually added to the control chart to allow changes in quality to be assessed quickly. Typically, warning limits are set at the overall mean ±2 standard errors of the means. If the warning limits are approached, it implies that changes are occurring that could lead to problems with product quality and action should be taken to restore the process to normal operation.

Action limits are set at the overall mean ±3 standard errors of the means. If the action limits are approached, then it is most probable that a statistically significant change to product quality has occurred and immediate action must be taken to address the problem. The standard error of the means is determined by calculating the standard deviation of a sequence of LOT means when the process is considered to be operating in statistical control. It is recommended that data from between 20 and 30 individual LOTS be used when computing the standard error of the means.

Typically, for latex condom production the standard error of the means, expressed as a percentage of the overall means, for burst volume and burst pressure data is in the region of 6%.

Any shift in the average burst pressure or volume of a LOT or LOTS by more than 18% to 20% almost certainly signals that there has been a highly statistically significant change in the manufacturing process and/or the materials used. If this occurs, further investigation is urgently required.

Monitoring changes in average burst volumes and pressures using control charts is an excellent method of detecting significant changes in the quality of production. This procedure can be implemented as an alternative to testing oven-conditioned condoms for bursting volume and pressure on a LOT-by-LOT basis.

Cumulative sum (cusum) control charts can also be used. In these charts, the cumulative difference between the actual result and the target or expected result is plotted in place of the process average. Cusum charts have advantage of being able to detect changes in underlying quality more rapidly than standard charts based on the process average, but they are more complex to construct and not quite so intuitive to understand.
Refer to a standard textbook on quality control procedures or statistics for more information on control charts. Procedures for producing these charts are also given in a series of ISO standards: *ISO 7870* is a general guide and introduction to control charts; *ISO 8245* describes Shewhart charts and includes techniques for charting attribute data; and *ISO 7966* describes acceptance charts. Cusum charts are described in parts 1–4 of *BS 5703*.

### 3. AGGREGATE ANALYSIS

On occasion, it might be useful to determine whether a shipment consisting of a number of lots is in compliance based on an aggregate assessment of the results taken across all the lots tested. In order to do this, the acceptance number for the total sample size may be calculated using the table below. The acceptance numbers (D) can be calculated from the following equations for any specific AQL and aggregated sample size (N). For additional advice on calculating and using these acceptance numbers, please contact the Help-Line.

When using the aggregate analysis method, it is also necessary to take into account the results for individual lots and the process average before reaching a decision about the capability of the manufacturer.

### 4. NUMBER OF LOTS REJECTED

Another approach is to review the number of lots rejected over the long term. If this number significantly exceeds 5%, there is a high probability that the manufacturer’s process average is greater than the stipulated AQL. A problem with this approach is that the number of lots that may fail in the short run will vary considerably and may exceed 5% because of the same type of sampling errors that apply to individual lots.

Therefore, this rule can only be applied to large numbers of lots. The sampling plans given in *ISO 2859–1* do, however, contain a useful guide that can be used to identify potential problems with quality in the short term.
These plans are primarily intended to be used with the switching rules which alter the probability of acceptance of LOTS on the basis of history. The switching rules are not generally used in the condom sector, but the rule for switching to tightened inspection is a very useful indicator of potential problems. This switch is triggered whenever there are two LOT rejections in any continuous sequence of five or fewer LOTS. If this occurs, the quality of all further LOTS from the manufacturer should be closely monitored and the procedures described in this annex should be used to determine the process average. Discontinuation of supply may be appropriate if this investigation confirms a serious quality problem.

Contact the Help-Line for further information:
qa-team-group@unfpa.org

\[
\begin{align*}
\text{AQL 0.25} & : D = 0.01(0.25N + 8N^{0.55}) \\
\text{AQL 1.0} & : D = 0.01(1.0N + 17N^{0.55}) \\
\text{AQL 1.5} & : D = 0.01(1.5N + 22N^{0.55}) \\
\text{AQL 2.5} & : D = 0.01(2.5N + 30N^{0.55}) \\
\text{AQL 4.0} & : D = 0.01(4.0N + 36N^{0.55})
\end{align*}
\]
Annex 3

Glossary of Terms and Abbreviations

**Acceptance number**
The highest number of non-compliers (failures) allowed in a specific test from a selected sample.

**AQL**
Acceptable Quality Limit. The quality level that is the worst tolerable process average when a continuing series of LOTS is submitted for acceptance sampling (ISO 2859–1). N.B. Manufacturers should be consistently achieving a process average that is better than the AQL.

**Batch**
Sometimes used in place of “LOT” (see definition of LOT). (WHO recommends that “LOT” be used when referring to condoms.) Can also refer to a homogenous quantity of latex that has been compounded and is ready for dipping from which several LOTS will be made. Or, to describe a quantity of individual raw materials.

**Bioburden**
The population of micro-organisms on a raw material, component, product, packaging or equipment.

**CE mark**
On condom packaging, a mark certifying that the product conforms to the essential requirements of the European medical device directive 93/42/EEC.

**Compliance testing**
A regime of testing to verify that a LOT complies with the specification.

**Condom**
Medical device that is intended to be worn on the penis during sexual activity for purposes of contraception and to prevent the spread of sexually transmitted infections. Condoms are usually made from natural rubber latex but may also be made from synthetic materials, such as polyurethane.

**Confirmatory testing**
Testing carried out on receipt of a product in country.

**Design Requirements**
Characteristics of the condom that are specified according to the procurer’s requirements.

**Expiry date**
The date at which the product is no longer considered acceptable for use.
<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection level</td>
<td>The degree of examination of the LOT, as specified in <em>ISO 2859–1</em>. The higher the inspection level, the more samples will be tested and, hence, the lower the risk of faulty products reaching the end user.</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization.</td>
</tr>
<tr>
<td>Length</td>
<td>The length of the condom measured from the open end to the tip, excluding any reservoir.</td>
</tr>
<tr>
<td>LOT</td>
<td>A quantity of condoms of a single grade, class, size and composition, manufactured under essentially the same conditions. With certain exceptions, all the condoms comprising a LOT will have identical formulation; the same dimension, colour, shape, and surface texture; be manufactured on the same production line; and be vulcanized under the same conditions.</td>
</tr>
<tr>
<td>National Regulatory Authority</td>
<td>A regulatory body with authority in a specific country to control the importation and distribution of medical products. See also <em>Regulatory authority</em>.</td>
</tr>
<tr>
<td>Package</td>
<td>The foil sachet in which the condom is sealed after manufacture.</td>
</tr>
<tr>
<td>Performance Requirements</td>
<td>The critical tests of quality that all LOTS must pass in order to provide adequate consumer protection.</td>
</tr>
<tr>
<td>Prequalification</td>
<td>The steps taken by the procurer to verify a manufacturer’s suitability to provide condoms of the required quality. The WHO/UNFPA Prequalification Scheme includes periodic assessment of manufacturing dossiers, testing of samples and factory inspection.</td>
</tr>
<tr>
<td>Pre-shipment compliance testing</td>
<td>A regimen of compliance tests carried out before a shipment leaves the supplier’s factory.</td>
</tr>
<tr>
<td>Process average</td>
<td>The percentage of condoms that is non-conforming over a defined time period or quantity of production. It is calculated for each requirement detailed in the <em>WHO/UNFPA Specification</em> by dividing the number of non-conforming condoms by the total number of condoms tested. Ideally, the process average for a specific attribute should be not greater than half the specified AQL.</td>
</tr>
</tbody>
</table>
Random sample
A sample of condoms drawn randomly from a LOT for testing purposes.

Regulatory authority
A national or international body set up to oversee the safety, efficacy and quality of medical devices, including condoms, imported and distributed within a country or region.

Sampling plan
A specific plan that indicates the number of units (condoms) from each LOT that are to be inspected (sample size) and the associated criteria for determining the acceptability of the LOT (acceptance and rejection numbers).

Shelf-life
The period of time after manufacture that the product is considered acceptable for use.

Specification
A detailed statement of a product’s requirements as established by the procurer. Usually, a specification is based on an established standard.

Standard
A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory authority.

Total Viable Count (TVC)
The number of living micro-organisms in a given sample.

UNFPA

USFDA
United States Food and Drug Administration.

Width
The dimension measured 30 mm from the open end, at a right angle to the length of the condom when it is unrolled and laid flat without any creases.

WHO
World Health Organization.

WHO/RHR
World Health Organization, Department of Reproductive Health and Research.