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<th>Description</th>
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<tbody>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use (EMA)</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency (<a href="http://www.ema.europa.eu">www.ema.europa.eu</a>)</td>
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<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>U.S. Food and Drug Administration (<a href="http://www.fda.gov">www.fda.gov</a>)</td>
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<tr>
<td>Health Canada</td>
<td>Federal department responsible for health product regulation in Canada (<a href="http://www.hc-sc.gc.ca">www.hc-sc.gc.ca</a>)</td>
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<tr>
<td>HPRA</td>
<td>Health Products Regulatory Authority, Ireland (<a href="http://www.hpra.ie">www.hpra.ie</a>)</td>
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<td>HSA</td>
<td>Health Sciences Authority, Singapore (<a href="http://www.hsa.gov.sg">www.hsa.gov.sg</a>)</td>
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<tr>
<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (<a href="http://www.ich.org">www.ich.org</a>)</td>
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<td>IGDRP</td>
<td>International Generic Drug Regulators Programme (<a href="https://www.igdrp.com">https://www.igdrp.com</a>)</td>
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<td>MHLW</td>
<td>Ministry of Health, Labour and Welfare, Japan</td>
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<td>Ph. Int</td>
<td>The International Pharmacopoeia (<a href="http://apps.who.int/phint/">http://apps.who.int/phint/</a>)</td>
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<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee (EMA)</td>
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<td>PMDA</td>
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<td>TGA</td>
<td>Therapeutic Goods Administration, Australia (<a href="http://www.tga.gov.au">www.tga.gov.au</a>)</td>
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<td>U.S.</td>
<td>United States of America</td>
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<td>WHO</td>
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<td>WHO MHP</td>
<td>WHO Access to Medicines and Health Products Division (<a href="http://www.who.int/medicines/en/">www.who.int/medicines/en/</a>)</td>
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<td>WHO RPQ</td>
<td>WHO Regulation and Prequalification Department</td>
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<td>WHO PQT</td>
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<tr>
<td>WHO HPS</td>
<td>WHO Health Product Policy and Standards Department</td>
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Note: The online version of this issue (freely available at www.who.int/medicines/publications/druginformation) has
Publication News

Publication of the *54th report of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) (WHO Technical Series, N° 1025).*

https://www.who.int/publications/i/item/978-92-4-000182-4

The WHO ECSPP advises the Director-General of WHO in the area of medicines quality assurance. It oversees the maintenance of *The International Pharmacopoeia* and provides guidance for use by relevant WHO units and regulatory authorities in WHO Member States to ensure that medicines meet unified standards of quality, safety and efficacy. The ECSPP’s guidance documents are developed through a broad consensus-building process, including iterative public consultation. Representatives from international organizations, state actors, non-state actors, pharmacopoeias and relevant WHO departments are invited to the ECSPP’s annual meetings, to provide updates and input to the Expert Committee’s discussions.

At its Fifty-fourth meeting, held from 14 to 18 October 2019 in Geneva, Switzerland, the ECSPP heard updates on cross-cutting issues from other WHO bodies, including the ECBS, the Expert Committee on the Selection and Use of Essential Medicines, the Local Production Programme, the MSM on substandard and falsified medical products, the PQT, the RSS unit and the INN team. Updates were also presented by partner organizations, including the IAEA, the PDG and UNICEF.

The EDQM updated the ECSPP on its activities as the custodian centre in charge of ICRS for use with monographs of *The International Pharmacopoeia*. Results from the latest phase of the EQAAS, which is organized by WHO with the assistance of the EDQM, were also presented.

The ECSPP reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in *The International Pharmacopoeia*. The Expert Committee adopted 13 guidelines and 16 pharmacopoeial texts (two general chapters, 13 new and revised monographs and one correction), omitted three pharmacopoeial texts, and confirmed the release of six new ICRS established by the custodial centre for use in connection with *The International Pharmacopoeia*.

The ECSPP also agreed to publish the outcomes of the WHO Biowaiver Project as an annex to its report; this will be a living document that will be updated as data become available.

The sections that follow summarize the specific decisions and recommendations made by the ECSPP during its Fifty-fourth meeting in 2019.
Guidelines and decisions adopted and recommended for use:

The following guidelines and decisions were adopted and recommended for use:

- Procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia (Annex 1);
- International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceuticals (Annex 2);
- Production of water for injection by means other than distillation (Annex 3);
- Good chromatography practices (Annex 4);
- Quality management system requirements for national inspectorates (Annex 5);
- Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance (Annex 6);
- Good storage and distribution practices for medical products (Annex 7);
- Points to consider for setting the remaining shelf-life of medical products upon delivery (Annex 8);
- World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices (Annex 9);
- World Health Organization/United Nations Population Fund technical specifications for male latex condoms (Annex 10);
- World Health Organization/United Nations Population Fund specifications for plain lubricants (Annex 11);
- WHO “Biowaiver List”: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (Annex 12); and
- WHO guideline on the implementation of quality management systems for national regulatory authorities (Annex 13).

Texts adopted for inclusion in The International Pharmacopoeia

The ECSPP adopted a series of texts, chapters and monograph, as listed next:

General texts
- Workplan 2020–2021

General chapters
- Polymorphism (new)
- Capillary electrophoresis (revision)
Monographs

General monographs for dosage forms and associated method texts
- Water for injections (revision)
- Ethanol/water mixtures in the reagent section (correction)

For antimalarial medicines
- doxycycline hyclate (revision)
- doxycycline capsules (revision)
- doxycycline tablets (revision)
- pyrimethamine (revision)
- pyrimethamine tablets (new)

For antibacterials, including antituberculosis medicines
- levofloxacin hemihydrate (revision)
- levofloxacin tablets (revision)

Other medicines for infectious diseases
- ciprofloxacin hydrochloride (revision)
- ciprofloxacin tablets (new)

Omissions
The ECSPP agreed to omit the following texts from The International Pharmacopoeia:
- undue toxicity (including the whole of Chapter 3.7 and all reference to the undue toxicity test in the monographs on kanamycin acid sulfate and kanamycin monosulfate);
- chlorpheniramine hydrogen maleate (monograph); and
- chlorpheniramine hydrogen maleate tablets (monograph).

International Chemical Reference Substances
The ECSPP confirmed the release of the following ICRS that have been newly characterized by the custodial centre, EDQM:
- metacycline ICRS 1
- artemether ICRS 3
- albendazole ICRS 1
- ethinylestradiol ICRS 4

The ECSPP also authorized the following chemical reference substances, established by the EDQM, for use according to the respective monographs in The International Pharmacopoeia:
- ciprofloxacin hydrochloride for peak identification
- levofloxacin for system suitability

***
Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities

DRAFT FOR COMMENTS

Please send your comments to Dr Valeria Gigante, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (gigantev@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 30 June 2020.

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

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities

1. Introduction and background


The WHO *Supplementary guidelines on good manufacturing practice: validation* were published in 2006 and were supported by seven appendices. In 2019, the WHO *Good manufacturing practices: guidelines on validation* (2) were updated and republished. Some of the seven appendices were also individually updated between 2013 and 2019:

- Appendix 1. Validation of heating, ventilation and air conditioning systems (3).
- Appendix 2. Validation of water systems for pharmaceutical use (4).
- Appendix 3. Cleaning validation (5).
- Appendix 4. Analytical procedure validation (6).
- Appendix 5. Validation of computerized systems (7).
- Appendix 7. Non-sterile process validation (9).

Appendix 3, relating to cleaning validation (5), was not updated at that time. Its revision, however, was discussed during an informal consultation held in Geneva, Switzerland, in July 2019. The outcome of the discussion was presented to the WHO Expert Committee on Specifications for Pharmaceutical Products (ECSPP) meeting in October 2019. The ECSPP acknowledged the importance of harmonization in regulatory expectations with regards to cleaning validation approaches. The Expert Committee recommended a “Points to consider” document be prepared in order to describe the current approaches used in cleaning validation and highlighting the complexities involved in order to establish a common understanding. A revision of the relevant appendix would then be considered by the Expert Committee thereafter.
Many manufacturers produce products in multi-product facilities where there is a risk of contamination and cross-contamination. Some of the main principles of good manufacturing practices (GMP) include the prevention of mix-ups and the prevention of contamination and cross-contamination. It is therefore important that manufacturers identify all risks for contamination and cross-contamination and identify and implement the appropriate controls to mitigate these risks. These controls include, for example, technical and organizational measures, dedicated facilities, closed systems, cleaning and cleaning validation.

2. Scope

The scope of this document is to discuss the different possible approaches – including methods that account for pharmacological and toxicological data (Health-Based Exposure Limits {HBEL}) – that could be used when establishing safe carryover limits when manufacturing in shared facilities.

This document further provides clarification on cleaning validation and presents points to consider when reviewing the current status and approaches to cleaning validation in multiproduct facilities. It reflects the current regulatory guidance and expectations. It further focuses on approaches where HBELs setting need to be considered in cleaning and cleaning validation approaches.

The principles should be applied in manufacturing facilities with active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs).

This document should be read in conjunction with the main GMP text and supplementary texts on validation (1-10).

3. Glossary

**cleaning validation.** Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

**contamination.** The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or an intermediate or pharmaceutical product during handling, production, sampling, packaging, repackaging, storage or transport.
**cross-contamination.** Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

**margin of safety.** The margin of safety is the distance between a calculated acceptance limit and the actual residues after cleaning. It indicates the probability that a patient has to be exposed to the API residues resulting from cleaning.

**maximum safe carryover (MSC).** Mathematically calculated quantity of residue from a previous product when carried over into a different product that can represent potential harm to the patients.

**maximum safe surface residue (MSSR).** The maximum safe surface residue is mathematically calculated dividing the quantity of residue on a contact surface by the total area of contact (Maximum Safe Carryover/Total Equipment Surface Area).

**verification.** The application of methods, procedures, tests and other evaluations, in addition to monitoring, in order to determine compliance with GMP principles.

### 4. Traditional approach

For details on the traditional approaches in cleaning validation, see the WHO Technical Report Series, No. 1019, Annexure 3, Appendix 3, 2019 (5).

One traditional approach is that cleaning validation is performed and the appropriateness of the cleaning procedure was based on acceptance criteria suggested in GMP texts. This approach may no longer be acceptable and justifiable as HBELs were not considered.

Where traditional acceptance limits are used, the decision should be discussed and justified as an alternative to new approaches in setting acceptance criteria.

In view of the risks of contamination and cross-contamination, the new approaches, as described below, should be implemented without delay.
5. **New approaches**

Traditional cleaning validation approaches were often based on verifying that a cleaning procedure was effective. However, in many instances, no development work or cleanability studies were performed for these cleaning procedures.

Manufacturers should ensure that their cleaning is effective and appropriate and that their cleaning validation provides scientific evidence that identified products can be manufactured in shared facilities – with control measures implemented to mitigate the risks of contamination and cross-contamination.

This approach should include at least the following points which are further described in the text below:

- cleanability studies;
- risk assessment and risk control;
- technical and organizational controls;
- HBELs setting;
- analytical procedures; and
- cleaning verification with proven capability through statistical evaluation.

Manufacturers should describe their policy and approaches, including the points mentioned above, in a document such as a master plan.

It is strongly recommended that manufacturers review their existing technical and organizational measures, suitability of cleaning procedures and appropriateness of cleaning validation. Genotoxic and carcinogenic substances, degradants and other contaminants should be identified and the appropriate action should be taken in order to ensure that materials and products are not contaminated when produced in shared facilities.

5.1 **Documentation**

Risk management principles, as described in other WHO guidelines on quality risk management (10), should be applied to assist in identifying risks and controls to mitigate contamination and cross-contamination.

Procedures, protocols, reports and other related and supportive documentation should be prepared, used and maintained.
The policy and approaches in cleaning and cleaning validation may be described in a Cleaning Validation Master Plan. Experiments and validation should be performed in accordance with predefined, authorized standard operating procedures, protocols and reports.

The design and layout of documents, and the reporting of data and information, should be in compliance with the principles of good documentation practices (11) and should also meet data integrity requirements (12).

5.2 Equipment

Consideration for cleaning validation should cover contact surfaces, as well as non-contact surfaces, where the latter have been identified as areas of risk.

Authorized drawings of equipment should be current, accurate and available. These should be used when equipment surface areas are calculated. Source data for these calculations should be available. The calculated values should be used in the calculations in cleaning validation.

Equipment and components that are difficult to clean, such as sieves, screens and bags, should also be included in the cleaning validation and calculations.

5.3 Detergents and solvents

Solvents and detergents used in cleaning processes should be selected with care. They should also be appropriate for their intended use. The selection of the relevant solvent and detergent should be justified.

There should be proof of effectiveness and appropriateness of the selected solvent and detergent.

Other points to consider include the concentration in which these are used, their composition, and removal of their residues after cleaning.

The use of solvents and detergents should be included in cleanability studies.
5.4 Sampling

Traditionally, cleaning validation included the sampling of equipment and other areas in order to determine whether or not there was any residue remaining on the surfaces. The focus was mainly on contact surface areas. Non-contact surface areas were sometimes considered by some manufacturers.

A combination of at least two or three sampling methods should be used. These include a combination of swab samples, rinse samples and visual inspection.

The appropriate sampling procedures and techniques should be selected and used to collect samples. These should be clearly described in procedures and protocols. The location (swab sample) and the manner in which the samples are collected should be clearly described and be scientifically justifiable.

The manner in which a rinse sample is collected should be described in detail. The procedure should be clear and unambiguous.

The manner in which samples collected are prepared for analysis should be appropriate and described in detail.

5.5 Cleanability studies

Before a cleaning procedure is validated and adopted for routine use, a cleanability study should be performed in order to determine the appropriateness of the procedure for removing material, product residue, cleaning agents and microorganisms.

The lowest concentration of a substance that can be removed by following the cleaning procedure should be established for different materials, intermediates and products on different materials of construction. The concentration can be expressed in mg/m2.

Cleanability studies should be described in authorised documents, such as protocols and procedures. The method should be scientific and may include spiking on coupons made from different materials of construction. The so-called beaker method, or other appropriate method, may be used.
Consideration should be given to all substances and different procedures where different processes or solvents are used, including different surface materials.

The results should be documented in authorized reports and used in further determinations, such as Maximum Safe Residue.

5.6 Risk assessment and risk control

Risk identification should be performed with a focus on the assessment of risks and defining and implementing controls to mitigate the risk of contamination and cross-contamination.

These should include technical and organization controls, including but not limited to, premises, equipment, utilities, containment, closed systems, cleaning and cleaning validation.

5.7 Technical and organizational controls

The appropriate technical and organizational controls should be defined and implemented.

Their appropriateness and effectiveness should be evaluated. Note: Cleaning and cleaning validation are considered additional and supplementary controls to technical and organizational controls.

Technical and organizational controls should be justifiable and clearly documented.

Technical controls, such as the design of the premises and utilities (e.g. heating, ventilation and air-conditioning [HVAC], water and gas), should be appropriate for the range of products manufactured (e.g. pharmacological classification, activities and properties).

Organizational controls, such as dedicated equipment, procedural control, and campaign production, should be considered where appropriate as a means to reduce the risk of cross-contamination.
5.8 Health Based Exposure Limits (HBELs) setting

Manufacturers should establish, document and implement a company-wide policy on HBELs setting for shared facilities.

APIs and products manufactured in shared facilities should be reviewed based on scientific evidence in order to determine whether production and control activities in shared facilities may be considered acceptable or whether dedicated facilities are required for the production and control of identified products.

This is applicable to legacy products as well as the introduction of new products introduced into a facility through a change control procedure.

Procedures should be established and implemented describing how scientific data and toxicological information on HBELs should be obtained.

Data and information should be gathered and presented in a report. The data should be free from bias. Where this service is outsourced, the appropriate measures should be put in place in order to ensure that the data obtained are reliable. GMP requirements, such as vendor qualification, agreements and other related aspects, should be considered.

The report should include scientific detail, including information on:
- chemical structure;
- hazard identification;
- mode of action;
- identification of critical effects;
- establishing NOAELs (no-observed-adverse-effect level);
- adjustment factors;
- pre-clinical, clinical and non-clinical data;
- pharmacokinetics and pharmacodynamics;
- expert assessment;
- identification of the critical effect;
- assignment of adjustment factors (AF);
- argumentation for the selected HBEL;
- routes of administration;
- point of departure (POD);
- justification for critical effect of POD; and
- justification for factor.
The Permitted Daily Exposure (PDE) should be calculated based on the data and information obtained. For example:

\[ PDE = \text{NOAEL} \times \text{weight adjustment} \]
\[ \times F_1 \times F_2 \times F_3 \times F_4 \times F_5 \]

Where NOAEL is no-observed adverse event level, and F represents various factors. The value selected should be justifiable.

The report should be reviewed by the manufacturer’s in-house team for completeness and appropriateness. Team members should have the appropriate qualifications and experience in the field of toxicology. A summary report should be prepared for each product and contain information on the PDE value, genotoxicity and carcinogenicity (13).

These scientific reports should be used when considering the cleaning validation control measures.

Manufacturers should periodically review and update PDE reports. The appropriate action should be taken where such a report needs to be updated.

### 5.9 Acceptance criteria

The limits established in cleaning validation should be justifiable.

Manufacturers often specified acceptance limits based on historical GMP texts. These traditional limits may no longer be acceptable as HBELs (PDE) and cleanability studies were not performed in many cases.

Criteria such as Margin of safety, Maximum Safe Carryover (MSC) and Maximum Safe Surface Residue (MSSR) values should be calculated. Calculations and data should be available and comply with data integrity principles. The calculation should include values of PDE, maximum daily dose, batch size and equipment surface areas.

MSSR should be calculated and presented, for example, in table form listing preceding and following product values. The cleanability value obtained should be considered in determining the acceptability of the procedure(s) and whether other controls including separate, dedicated facilities are required. (See Annex 1 as an example.)
5.10 **Grouping by therapeutic use**

The risk associated with contamination and cross-contamination from one product to another product in one therapeutic group, and between products in different therapeutic groups in shared facilities, should be considered. For example, due to the risk, certain products should be manufactured in dedicated or segregated self-contained facilities, including certain antibiotics, certain hormones, certain cytotoxics and certain highly-active drugs – even though these are in the same therapeutic class.

The risk assessment should include, for example, PDE values, batch size, maximum daily dose of the next product, as well as other criteria associated with cleaning.

The higher the PDE value, the lower the risk. The products and therapeutic groups considered for manufacturing should be plotted based on an identified scale of risk (14, 15). An illustration is presented in figure 1 where hazard is plotted against risk.

*Figure 1.* Increasing hazard and PDE values

![Increasing hazard](image)

- Health Based Exposure Limit (HBEL) – PDE
- >10 000ug/day
- <10ug/day

5.11 **Analytical procedures**

Samples obtained in cleaning validation should be analyzed by using specific, validated procedures. The procedures should be developed, validated and appropriate for their intended use.

Specific methods, such as HPLC, should be used where possible. Non-specific methods including UV spectrophotometry should only be used where specific methods cannot be employed.

Testing for total organic carbon (TOC) may be used where indicated and where justified.
Analytical procedures validation should be done on-site. Where analytical procedures were developed and validated off-site, the scope and extent of validation should be defined and justified. This includes procedures that are transferred from research and development laboratories to site laboratories. (For analytical procedure validation, see reference 6.)

Manufacturers should ensure that the procedures remain in a validated state.

5.12 **Data integrity**

Data, information and results pertaining to, for example, HBELs, PDE reports, results obtained from cleaning validation and calculations should be scientific and should be in compliance with the principles as contained in data integrity guidelines (12).

5.13 **Cleaning validation and cleaning verification**

The cleaning procedure should be validated after the cleaning procedure had been developed and the cleanability study had been done.

Cleaning validation should include proof of, for example, the applicability of the procedure to clean equipment that:
- had been kept in an unclean state for a period of time (dirty equipment hold time);
- are used after product changeover;
- are used in a campaign, where multiple batches of a product are produced one after the other; and/or
- are stored in a clean state for defined periods of time (clean equipment hold time).

Cleaning validation should include consideration of HBELs when the appropriate method used in establishing carryover limits. Where HBELs are not used, scientific justification should be provided.

The company should describe the policy and approach to cleaning verification. The effectiveness of the validated cleaning procedure should be routinely verified. The approach may include swab or rinse samples. The results obtained from testing on a routine basis should be reviewed and subjected to statistical trending.
5.14 Visually clean

Visually clean is an important criterion in cleaning validation and should be one of the acceptance criteria used on a routine basis. Visible residue limits (VRLs) should be determined. The process to determine the limit should be appropriately described in procedures and protocols including concentrations, method of spiking, surface areas, material of construction and other conditions such as light and angles.

VRLs should be quantitatively established for APIs, excipients, detergents and pharmaceutical products.

The Visual Detection Index (VDI) may be calculated using MSSR.

5.15 Cleaning verification and process capability

The cleaning procedure should remain in a validated state. Cleaning verification and process capability may be used to provide data to support this. For example, the results from cleaning verification sample analysis could be statistically trended. The capability of the cleaning process is then calculated through an appropriate statistical process.

The presentation of individual results and data used in the calculation, such as with a Central Processing Unit (Cpu) and acceptable daily exposure (ADE) base limit, should meet ALCOA principles.

Data should be presented, for example, in graph form, and the capability of the process in relation to control limits and the margin of safety should be discussed as part of continuous improvement.

5.16 Personnel

Personnel should be trained in the principles of cleaning validation, with an emphasis on contamination and cross-contamination control, HBELs setting, equipment disassembly, sampling, testing and statistical calculations.
5.17 Quality metrics and performance indicators

Aspects of HBELs setting, cleanability studies, cleaning validation and cleaning verification, as well as process capability, should be considered in quality metrics, with performance indicators identified and to be monitored.

5.18 Life cycle

HBEL reports, protocols, cleaning validation and cleaning verification should be included in a company policy and life cycle approach in preventing cross-contamination in shared facilities.
References


Further reading

Annex 1. Using HBELS to assess risk in cleaning validation*

Example of calculating MSC and MSSR, using HBELs, to determine the risks associated with cleaning validation. It can also give an indication of the acceptability, or not, of manufacturing specified products in shared facilities.

Step 1. Calculate MSC

\[ \text{MSC} \ a \ (g) = \text{PDE} \ a \ (\mu g) \times \text{Batch size} \ b \ (kg) \times \text{Maximum Daily Dose} \ b \ (mg) \]

Where

- \( a \) = product \( a \)
- \( b \) = product \( b \) or subsequent product

Step 2. Tabulate the data

<table>
<thead>
<tr>
<th>API</th>
<th>PDE \ (\mu g/day)</th>
<th>MDD \ (mg/day)</th>
<th>Batch size \ (Kg)</th>
<th>Equipment surface \ (m^2)</th>
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<tr>
<td>1</td>
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Step 3. Calculate MSSR \ (mg/m^2)

\[ \text{MSSR} = \frac{\text{MSC} \ a \ (g) \times 1000}{\text{Surface for} \ b \ (m^2)} \]

Step 4. Tabulate the data for MSSR and identify where there is a risk, based on the MSSR that are not met when considering the cleanability of the procedure.

<table>
<thead>
<tr>
<th>MSSR</th>
<th>Following product b</th>
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<tr>
<td></td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Pre-Ce-ding</td>
<td></td>
</tr>
<tr>
<td>Product a</td>
<td></td>
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World Health Organization/United Nations Population Fund Recommendations for condom storage and shipping

DRAFT FOR COMMENTS

Please send your comments to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 20 August 2020.

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World Health Organization/United Nations Population Fund Recommendations for condom storage and shipping

Background

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As agreed at the ECSPP meeting in October 2018, the United Nations Population Fund (UNFPA) and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms and are developing seven different documents:

- prequalification programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices;
- technical specifications for male latex condoms;
- specifications for plain lubricants;
- condom quality assurance;
- guidance on testing of male latex condoms;
- recommendations for condom storage and shipping temperatures; and
- guidance on conducting post-market surveillance of condoms.

All seven documents were restructured and revised in the first half of 2019, then sent to the EAP and put out for public consultation in July 2019. The comments received were reviewed by a group of specialists in October 2019, prior to being presented to the ECSPP. At UNFPA’s request, the ECSPP focused on the first three documents (on UNFPA’s Prequalification Programme guidance, condom quality assurance and specifications for plain lubricants), noting that all comments have been addressed. It suggested some further minor revisions, including recommending changes to clarify that, while the specifications for plain lubricants are principally targeted at procurement agencies, they may also be used by regulators for public procurement. The next steps for the remaining four documents include incorporating comments from the latest consultations and then bringing them back to the ECSPP for possible adoption at its next meeting in 2020.
1. **During shipment**

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

The average mean kinetic temperature\(^1\) (MKT) 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. Ideally, data loggers can calculate the mean kinetic temperature either automatically or by using software supplied with the data loggers after data has been downloaded.

2. **Warehouse storage**

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

Long-term (i.e. one month to a year) average storage temperature should be less than 30 °C. Short-term (i.e. up to one month) temperature excursions should not exceed 40 °C. The recommended limit for short term exposure is cumulative over the total period of storage.

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 +5/ -2 °C) because this is the MKT of the most extreme climate in climatic zones III and IV\(^3\). 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 + 5/ -2 °C as the storage temperature for stability studies, is given in the Technical Basis Paper of the WHO/UNFPA *technical specifications for male latex condoms* (3).

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\(^1\) Temperatures during shipping can be monitored using data loggers. Most modern data loggers can automatically calculate and print out the mean kinetic temperature (MKT) (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 MKT. If, during shipping, the MKT exceeds 30 °C and/or peak temperatures exceed 50 °C, a risk assessment should be conducted to assess whether or not the properties of the condoms in the consignment have been compromised. Random sampling and testing of condoms for burst properties is recommended to support the risk assessment.

\(^3\) More details on the climatic zones can be found in *WHO Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (5)
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 shipping 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. It should be ensured that the floor of the storage area is paved with concrete and the walls and floor should not get damp due to seepage of water or rain water condensate. The ambient temperature in the warehouse should be recorded.

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).

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


Further reading

World Health Organization/United Nations Population Fund
Guidance on conducting post-market surveillance of condoms

DRAFT FOR COMMENTS

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Guidance on conducting post-market surveillance of condoms

Background

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As agreed at the ECSPP meeting in October 2018, the United Nations Population Fund (UNFPA) and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms and are developing seven different documents:

- prequalification programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices;
- technical specifications for male latex condoms;
- specifications for plain lubricants;
- condom quality assurance;
- guidance on testing of male latex condoms;
- recommendations for condom storage and shipping temperatures; and
- guidance on conducting post-market surveillance of condoms.

All seven documents were restructured and revised in the first half of 2019, then sent to the EAP and put out for public consultation in July 2019. The comments received were reviewed by a group of specialists in October 2019, prior to being presented to the ECSPP. At UNFPA’s request, the ECSPP focused on the first three documents (on UNFPA’s Prequalification Programme guidance, condom quality assurance and specifications for plain lubricants), noting that all comments have been addressed. It suggested some further minor revisions, including recommending changes to clarify that, while the specifications for plain lubricants are principally targeted at procurement agencies, they may also be used by regulators for public procurement. The next steps for the remaining four documents include incorporating comments from the latest consultations and then bringing them back to the ECSPP for possible adoption at its next meeting in 2020.
1. **Introduction**

Good quality condoms conforming to the *World Health Organization (WHO)/United Nations Population Fund (UNFPA) technical specifications for male latex condoms* (3) 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 still conform to the requirements of the *World Health Organization/United Nations Population Fund technical specifications for male latex condoms* (3) and *ISO 4074, Natural rubber latex male condoms – Requirements and test methods* (5). Surveillance testing may also be conducted to determine if there has been a significant deterioration in condom properties relative to retained samples kept under controlled conditions.

It is recommended that prequalified manufacturers conduct periodic surveillance testing on condoms that are nearing their expiry date and have been stored in hot regions to support the shelf-life claims made on the basis of real time and accelerated stability studies. 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 schemes given in Annex B of ISO 4074 (5) should be used. If possible, samples should be taken from at least three lots from each manufacturer to give an indication about lot-to-lot homogeneity. If multiple lots from a single manufacturer are being evaluated, then the sampling schemes of Annex A of ISO 4074 (5) 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 an adequate number of samples from one batch is not available at any particular retail outlet or clinic, it may be possible to hunt down and get some more samples of the same batch from a nearby retail store or clinic in the region.

If sample sizes are restricted, then they should still be selected from ISO 2859-1, *Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality level (AQL) for lot-by-lot inspection – Amendment 1* (6). Whenever possible, select sampling schemes 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 (6) for the operating characteristic curves and acceptance probabilities of the sampling schemes). Use sample sizes that are consistent with ISO 2859-1 (6). Sample sizes that fall between the specified sample sizes in the tables should not be used (for example, Table II-A). Doing so can result in situations where it is not possible to make a statistically valid decision about whether or not the product sampled conforms to the specification. If there are insufficient samples available to use a specified sample size, the next lowest specified sample size, for which there are enough samples and corresponding to that AQL, should be used.

For performance requirements, such as burst properties, freedom from holes and package integrity, avoid zero accept sampling schemes whenever possible (for example, a sample size of 50 for an AQL of 0.25 with an acceptance number of 0). These sampling schemes generally have poor operating characteristic curves which can lead to type I and type II errors (i.e. an 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 to use zero accept sampling schemes, due to a shortage of samples, 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 the expiry date noted for each lot sampled. If possible, samples from the different lots that are to be combined should be kept separate throughout the testing process in order 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 the transport arrangements needed to deliver the condoms to the laboratory should be considered. It is essential to ensure that the condoms will not be subjected to any adverse conditions in transit that could affect the results of the tests. Sending samples by air freight 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**

The laboratories used for surveillance testing shall be accredited to *ISO 17025* (7) 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 re-tested if necessary.

For more information about the selection of laboratories, please refer to *World Health Organization/United Nations Population Fund Condom quality assurance* (8).

When selecting test laboratories, consideration should also be given 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. One should confirm with the laboratory whether or not there are any rules relating to the import of samples for testing prior to sending the samples.

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 polymodal) distributions of burst pressure and/or volume are indicators of poor homogeneity within the lot. In some cases, this might indicate that the product is substandard and/or falsified; for example, the lot in question may consist of mixed condoms from different lots or even condoms from different manufacturers. If substandard and falsified medical 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. Producers of substandard and falsified medical products commonly make small mistakes with labelling so return samples of the packaging, and any information received, with the product to the manufacturer for checking. Following confirmation from the manufacturer that the product is falsified, inform the WHO team working on substandard and falsified medical products at rapidalert@who.int
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 *World Health Organization/United Nations Population Fund Condom quality assurance*, Annex 2 (8), 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.
References


World Health Organization/United Nations Population Fund

Guidance on testing of male latex condoms

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1. Introduction

Condoms, procured as part of a public procurement programme or otherwise, are tested as per the World Health Organization (WHO)/United Nations Fund Population (UNFPA) specification by independent laboratories. In addition, there may be specific programme requirements which would have been incorporated in the purchase orders. These testing laboratories have to be accredited to ISO 17025:2017, General requirements for the competence of testing and calibration laboratories (5), for the test methods in ISO 4074:2015, National rubber latex male condoms – Requirements and test methods (6), in order to be considered for testing services. The following guidance has been developed to assist the laboratories to standardize testing and reduce variability. This guidance is meant to supplement the information on conducting the tests specified in ISO 4074:2015 (6).

2. Determination of length (ISO 4074:2015, Annex D)

Condom length can be measured manually, 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 for the correct handling of the data and regularly calibrated following the methods recommended by the manufacturer.

A standard mandrel, described in ISO 4074:2015 (6), 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 the 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 without removing the lubricant 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 all 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. While fixing the length mandrel, it should be ensured that it is fixed on a horizontal plane without slanting.

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


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 for correct handling of the data 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 without removing the lubricant 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.

*ISO 4074:2015* (6) 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 poor. One of the reasons for this is to accommodate condoms where the surface is not smooth and, also, it is thought that the pressure applied by the foot of the micrometer to ensure good contact with the material under test can compress the film slightly. In some cases, this pressure has also been found to be well outside the specified 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. For textured condoms, the thickness is usually measured using micrometer method at the point specified and agreed between the manufacturer and the buyer of the condoms.

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 measuring 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.
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 (5), test equipment shall “be safeguarded from adjustments which would invalidate the test result”. It is therefore recommended that parts of the gauge that should not be adjusted during routine use, such as the gauge mount, are made temper-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;
- any corrections for variations in atmospheric pressure owing to the altitude of the test laboratory;
- cleanliness of the air supply hole in the mandrel;
- maintenance of the supply air pressure and the air flow rate; and
- maintenance of the air temperature from the compressor.

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.

*Note:* 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. Some burst testing machines release the condom as soon as inflation is stopped. If this function cannot be temporarily disabled for calibration purposes, it may be necessary to mark the correct inflation length on the condom first.
- Measure the length of the condom to the mark using the condom length measuring mandrel described in Annex D of ISO 4074:2015\(^{(6)}\). 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 if the machine has inflation cuffs that do not leak air into the condom, 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. If the testing machine does not permit the cuff to remain inflated when the air supply is turned off, a systematic difference between the volume readings for different test heads may indicate that a cuff is leaking.

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 dm³/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 4074:2015(6) 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 every day, depending on the number of test heads on the machine, 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.
5.7 **Cleanliness of the air supply hole in the mandrel**

It should be ensured that the air supply point in the mandrel be cleaned regularly to avoid partial blockage by accumulated powder and lubricant.

5.8 **Maintenance of the supply air pressure and the air flow rate**

It is recommended that a dedicated air compressor is provided for the inflation tester. Using a compressor which may not have adequate capacity to meet with the demand of maximum use by other operations in the laboratory could cause the air pressure in the inflation tester to have momentary fluctuation and variations from the time of daily calibration checks.

5.9 **Maintenance of the air temperature from the compressor**

It is recommended that the air compressor for inflation tester is located in such a manner that it is not subject to extreme variations during the operation during the day, which could affect the density of the air.


It is a requirement of *ISO 4074:2015 (6)* 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 (6).*
The following are points to note when conducting these aging studies:

- The condoms used in the studies must comply with the requirements of ISO 4074:2015 (6). 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. *ISO 4074:2015 (6)* specifies that this period shall not exceed two years. WHO/UNFPA technical specifications, however, specify a maximum storage period of six months. By agreement with UNFPA, it is acceptable for manufacturers to conduct stability studies on condoms that have been stored for six months between dipping and packaging to verify shelf-life claims for procurement under the WHO/UNFPA prequalification scheme.

- Some manufacturer’s formulation may require a certain time period of maturation of condoms before their burst properties could stabilize. It is recommended to allow the required maturation time before the condoms are foiled and this minimum maturation time be validated and applied while conducting stability studies.

- Minimum stability requirements (clause 11.2) (6) must be established.

- Three different lots of condoms must be used in the studies. These production lots from where samples are drawn for stability studies should represent the actual normal commercial batch sizes of the manufacturer and not just three sub-lots of the manufacturer.

- 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 a 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 or six months to comply with UNFPA requirements, as noted above.
• Monitor the physical properties of the condoms at intervals during the real-time study. Two methods are described in clause K.2.4 (6) 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, carry out necessary investigation and analyse the root cause of failure. Investigation could also be carried out by analysing more samples from that batch representing that time point. If root cause is common to the other two batches as well, the stability studies should be stopped. If there are no assignable causes for variation at any one specific time point, the study can continue but must be stopped if more than one set of samples fail. At the end of the proposed or claimed shelf-life, carry out the test with larger sample sizes as per the requirements of ISO 4074:2015 (6).
  ❖ 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 (6)), 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 (6).

• 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 (6).

• Existing condoms whose shelf lives were established following the procedures of earlier versions of ISO 4074 (i.e. 2002 (7) and 2014 (8)) can be considered to be compliant. However, considering the several changes that have taken place between 2002 and now, the manufacturer should initiate fresh real time stability studies as per the requirements of ISO 4074:2015 (6), for the products that are currently being manufactured.

• 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, Rubber condoms – Guidance on the use of ISO 4074 in the quality management of natural rubber latex condoms (9), 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, the reasons for this decision and all supporting test data shall be documented.
7. **Freedom from holes**

7.1 *ISO 4074:2015, Annex M*

The *ISO 4074:2015* 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 dm³.
- 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 (WHO/UNFPA do not recommend rolling more than 10 revolutions).
- 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 and/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. In addition to calibration, the equipment and the technique should be verified on routine basis for effectiveness in detecting the holes.

• 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 described in the Water Leak Test. Note that ISO 4074:2015 (6) specifies the Hang and Roll method must be used - not the ASTM D3492 Hang and Squeeze method (10).

• Note that the condoms have to be observed during filling in order to detect any holes (see M 3.3.7, third line (6))
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 ASTM D3492 (10) 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 ASTM Standard (10).
- 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 tests for Freedom from Holes and Visible Defects.

The individual sealed containers are examined by visual observation for any visibly open seals. Defects may include improperly formed seals, condoms getting trapped in sealing area, uneven or very narrow sealing edges leading to open seals and leakages. However, it should be noted that these packaging “defects” are not specified in ISO 4074:2015 (6).

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 the 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 (6) 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. It is recommended to have a display of specific visual defects in the laboratory for the operators to easily identify and classify the defects.


Unless specified otherwise in the procurement contract and purchase order, the Package Integrity test specified in Annex N of ISO 4074:2015(6) shall be used to test package integrity. For condoms intended for distribution to high altitude regions or to be distributed by air freight, the alternative “dry vacuum method” described in Annex 2 of the revised World Health Organization/United Nations Population Fund Technical specifications for male latex condoms(3) may be specified.

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4 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.
When conducting the test according to the method specified in Annex N of ISO 4074:215 (6), the following points should be noted:

- 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 ± 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.
- 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.
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).
References


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Good reliance practices in regulatory decision-making:
high-level principles and recommendations

DRAFT FOR COMMENTS

Please send your comments to Mrs Marie Valentin, Technical Officer, Regulatory Convergence and Networks, Regulation and Safety (valentinm@who.int), with a copy to Mrs Carolyn Doucelin (doucelinc@who.int) before 24 July 2020.

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

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Good reliance practices in regulatory decision-making:
high-level principles and recommendations

1. Acronyms

**ACSS**  
Australia-Canada-Singapore-Switzerland Consortium

**AMRH**  
African Medical Products Regulatory Harmonisation

**APEC**  
Asia-Pacific Economic Cooperation

**API**  
Active Pharmaceutical Ingredient

**ASEAN**  
Association of Southeast Asian Nations

**AVAREF**  
African Vaccine Regulatory Forum

**CEP**  
Certificate of Suitability to the monographs of the European Pharmacopoeia

**CPQ**  
Confirmation of active pharmaceutical ingredient Prequalification

**COFEPRIS**  
Comisión Federal para la Protección Contra Riesgos Sanitarios (Mexico)

**CRP**  
Collaborative Registration Procedure

**EAC**  
East African Community

**ECOWAS**  
Economic Community of West African States

**ECSPP**  
Expert Committee on Specifications for Pharmaceutical Preparations

**EMA**  
European Medicines Agency

**EU**  
European Union

**EU-M4 all**  
European Union Medicines for all

**GBT**  
Global Benchmarking Tool

**GCP**  
Good Clinical Practices

**GMP**  
Good Manufacturing Practices

**GRP**  
Good Regulatory Practices

**GRelP**  
Good Reliance Practices

**ICH**  
International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

**IMDRF**  
International Medical Device Regulators Forum

**IPRP**  
International Pharmaceutical Regulators Programme
MAGHP  Marketing Authorization for Global Health Products
MERCOSUR  Southern Common Market
MDSAP  Medical Device Single Audit Program
NRA  National Regulatory Authority; for the purpose of this document, this term also includes regional regulatory authorities such as the European Medicines Agency (EMA)
OMCL  Official Medicines Control Laboratories
PAHO  Pan American Health Organization
PANDRH  Pan American Network for Drug Regulatory Harmonization
PIC/S  Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
ASEAN PPWG  ASEAN Pharmaceutical Products Working Group
REC  Regional Economic Communities in Africa
SEARN  South-East Asia Regulatory Network
SADC  Southern African Development Community
SRA  Stringent Regulatory Authority (1)
UHC  Universal Health Coverage
WAHO  West African Health Organization
WHO  World Health Organization
WLA  WHO Listed Authorities
WHO-NNB  WHO-National Control Laboratory Network for Biologicals
2. Background

The World Health Organization (WHO) supports the implementation of reliance on other regulators’ work as a general principle in order to make the best use of available resources and expertise. This principle enables leveraging the output of others whenever possible while placing a greater focus at the national level on value added regulatory activities that cannot be undertaken by other authorities, such as in-country vigilance activities and oversight of local manufacturing and distribution. Reliance approaches facilitate timely access to safe, effective and quality-assured medical products and can help in regulatory preparedness and response, particularly during public health emergencies.

Good Reliance Practices (GRelP) are anchored in the overarching Good Regulatory Practices (GRP) (2) which provide a means for establishing sound, affordable and effective regulation of medical products as an important part of health system strengthening. If implemented effectively, GRP can lead to consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes.

An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating national regulatory authorities (NRAs) and designating those that meet a specific standard as WHO-Listed Authorities (WLAs) (3). Based on benchmarking using the WHO Global Benchmarking Tool (GBT) (4), WHO will assess the NRA’s regulatory performance and maturity level in order to qualify an NRA as a WLA and thereby provide a globally recognized, evidence-based and transparent system that can be used by NRAs as a reference to practise reliance.

The WHO held a consultative meeting in September 2019 in order to solicit input on the nature, structure and overall content of a document outlining GRelP. The meeting concluded that the Pan American Health Organization (PAHO)/Pan American Network for Drug Regulatory Harmonization (PANDRH) concept note and recommendations on regulatory reliance principles (5) should be used as a starting point for the development of a WHO GRelP document. The high-level document would be complemented in a second step by a repository of case studies, practice guides and examples of practical applications of GRelP.
3. Introduction

The United Nations Sustainable Development Goals and the drive for Universal Health Coverage (UHC) require that patients have access to quality-assured medical products, hence, strong regulatory systems for medical products remain a critical element of well-functioning health systems and an important contributor to improving access and ultimately achieving UHC.

It is widely recognized, however, that regulatory systems can be very resource-intensive. Establishing and sustaining mature regulatory systems is a high resourced enterprise that requires skilled human resources and significant public investments. Moreover, the globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have led regulators to recognize the importance of international cooperation in order to ensure the safety, quality and efficacy of locally used products. In view of the extent and complexity of regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative and more effective forms of collaboration in order to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where most needed.

Reliance represents a smarter way of regulating medical products in a modern regulatory world. Towards this end, countries are encouraged to formulate and implement strategies to strengthen their regulatory systems consistently with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance brings benefit to the industry, patients and consumers, national governments, as well as the donor community, and international development partners by facilitating and accelerating access to quality medical products.

There is a long history of enhancing the efficiency of regulatory systems through reliance. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (6), introduced by WHO in 1969, is a form of reliance providing assurance to countries participating in the Scheme about the quality of pharmaceutical products. The European Union (EU) introduced the mutual recognition procedure for marketing authorizations between Member States in 1995, and outcomes of Good Manufacturing Practice (GMP) inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) and mutual recognition agreements.
The use of reliance was more recently investigated by WHO through a survey conducted on behalf of the International Pharmaceutical Regulators Programme (IPRP) (7). The results showed that regulatory reliance is a broadly accepted and widely practiced approach in the area of medical products, especially among the participating well-resourced regulatory authorities. At the same time, responses also reflected an evolving situation marked by varying degrees of experience and promise in the use of reliance-based approaches. While the use of reliance in some regions may be characterized as an emerging trend, the commonly stated goals are to bring efficiency, to help strengthen regulatory systems and to optimize the use of resources. The results and suggestions from this survey were taken into account for the preparation of this document.

Given the increased prevalence and importance of reliance in the regulation of medical products, countries have requested WHO to develop practical guidance on the topic while ensuring that approaches meet the intended objectives. This document, and the companion documents that will follow, are intended to assist countries in implementing a sound, evidence-based and effective approach to reliance.

4. Purpose

The objective of this document is to promote a more effective and efficient approach to regulation as part of a “smart regulation” approach, thereby promoting access to quality-assured medical products.

It aims at presenting the overarching principles under which regulatory reliance in the field of oversight of medical products should operate and use reliance as a tool for effective regulation and regulatory system strengthening.

This document is intended to provide high-level guidance, definitions, key concepts and considerations in order to guide reliance activities, illustrative examples of reliance approaches and conclusions. It will be complemented by a “reliance toolbox” consisting of practice guides, case studies and a comprehensive repository of examples.
5. **Scope**

This document covers reliance activities in the field of regulatory oversight of medical products (i.e. medicines, vaccines, blood and blood products and medical devices including in-vitro diagnostics), addressing all regulatory functions spanning the full life cycle of a medical product.

In addition, this document is intended for all NRAs, irrespective of their level of maturity or resources, as well as policy makers, governments, the industry and other developers of medical products, and other relevant stakeholders.

6. **Definitions and key concepts**

6.1 **Definitions**

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance related to reliance. In addition to the definitions provided below, reference is made to the WHO Guideline on good regulatory practices: Guidelines for national regulatory authorities for medical products (2), which includes definitions for harmonization, convergence and other relevant terms.

**abridged regulatory pathways.** Abridged regulatory pathways are regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. Normally this would also involve some degree of work by the relying NRA (see “risk-based approach”, p. 13 ). The expectation is that the use of reliance in these pathways would save resources and shorten the timelines compared to the standard pathways, while ensuring that the standards for regulatory oversight are maintained.

**assessment.** For the purpose of this document, the term “assessment” covers the outcome of any evaluation conducted for a regulatory function (e.g. evaluation for a clinical trial application, evaluation of an initial authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection, etc.).
**equivalence of regulatory systems.** Equivalence (or comparability) of regulatory systems implies a high degree of similarity between two regulatory systems as established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international guidelines and standards, experience gained through the use of assessments for regulatory decision-making, joint activities and exchange of staff, among others. The expectation is that equivalent regulatory systems should lead to similar standards and levels of regulatory oversight or “level of control”.

**joint activity.** A joint activity is a process whereby a regulatory function is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other’s expertise and discuss any shortcomings of the data being evaluated. For example, a joint assessment is a procedure in which the same application is simultaneously submitted to two or more NRAs in order for the (assigned) NRAs to conduct their evaluations in parallel and share their respective scientific assessments with each other. The NRAs participating in the joint assessment can combine their list of questions or deficiencies to send to the manufacturer and base their respective independent regulatory decision on the outcome of these assessments. Similarly, a joint inspection is an inspection involving two or more NRAs sharing the activities and assessment performed during an inspection.

**recognition.** The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority is sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

**reference regulatory authority.** For the purpose of this document, the reference regulatory authority is a national or regional authority being relied upon by another regulatory authority.

**reliance.** The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.
**work-sharing.** Work-sharing is a process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include but are not limited to: jointly assessing applications for authorization of clinical trials, marketing authorizations or product manufacturing site inspections, joint work in the post-marketing surveillance of medical product quality and safety, joint development of technical guidelines or regulatory standards, and collaboration on information platforms and technology. Work-sharing also entails the exchange of information consistent with the provisions of existing agreements and compliant with each agency’s or institution’s legislative framework for sharing such information with other NRAs.

### 6.2 Key concepts

The diagram below illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiencies in their regulatory operations and how they avoid duplication by increasing the use of reliance approaches.
**reliance versus recognition.** Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or any other authoritative information available from other authorities and institutions. Recognition may be seen as a special and more complete form of reliance whereby one regulatory authority relies on the decisions of another regulatory authority, system or institution, obviating the need for additional regulatory assessment in reaching its own decision. Recognition usually requires formal and enabling legal provisions.

**unilateral vs. mutual reliance/recognition.** Reliance can be unilateral, for example, when a country chooses to rely on the assessment from another country unilaterally and without reciprocity. In other cases, reliance may be based on binding mutual agreements or treaties negotiated at the level of governments. These agreements may take considerable time and resources to set up as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation. The demonstration of equivalence (or comparability) of regulatory systems is normally a prerequisite to mutual reliance and recognition.

**life cycle approach.** The concept of reliance for regulatory oversight of medical products can be applied across the full life cycle of medical products, from clinical trial authorization to marketing authorization, including post-authorization procedures, vigilance, inspections, testing and lot release. While reliance approaches are widely used for the initial authorization of medical products, it is equally important to consider the use of reliance for pharmacovigilance and post-authorization activities given the substantial regulatory resources required for evaluating safety and variations over the product life cycle. Reviewing post-authorization changes to a product approved by a different authority may present some challenges. Therefore, if an NRA has relied upon another NRA’s decision for its initial approval, there is a strong benefit for similar reliance measures for post-authorization changes and pharmacovigilance activities. This also avoids the situation of different changes being accepted in the originating and receiving countries over time.

Reliance has also been shown to offer significant advantages in avoiding duplication in the field of inspections and lot release between countries.
risk-based approach. Each NRA should define its own strategy regarding the appropriate risk-based approach to reliance that considers factors, such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country, and opportunities for reliance. Using marketing authorization as an example, one could envisage four models and levels of reliance involving an increasing degree of additional assessment by the relying NRA:

- Confirmation of sameness of the product to ensure that the medical product is the same as the one that had been assessed by the reference regulatory authority.
- Verification of applicability of the assessment outcomes of another authority for regulatory decision-making in the national context, for example, in terms of legal and regulatory settings, benefit-risk assessment, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability.
- Abridged assessment of the quality, safety and efficacy/performance data taking into account information in the assessment reports of the reference regulatory authority.
- Joint assessment or work-sharing between two or more regulatory authorities. This could take various forms, including a primary review by one authority followed by a joint assessment session to finalize the assessment report and comments, or a distribution of the different modules (quality, non-clinical and safety/efficacy) between authorities.

Similar models can also be developed or used for other regulatory functions (e.g. inspection).

regional reliance mechanisms. In some regions, an assessment for medical products can be conducted centrally based on a regional regulatory system for a group of countries. The decision is then implemented in all the countries that are part of the regional system, such as the authorization system in the EU, the Gulf Health Council (GHC) and the Caribbean Regulatory System (CRS).
7. Principles underpinning good reliance practices

In developing a strategy on the use of reliance in regulatory functions, an NRA should consider possible approaches in the context of the needs and characteristics of the national health and regulatory system. The decision to practice reliance should take into consideration the existing capacities, regulatory systems’ needs, the availability of an authority that the NRA can rely upon with confidence, and how reliance can complement these capacities to drive efficiencies and the optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy seeking to make the best use of the available resources in any given setting. This would allow the allocation of resources to other areas of regulatory functions, such as vigilance and post-authorization activities, and increase the effectiveness of the local regulatory oversight. In addition, reliance can lead to more evidence-based and better quality decisions.

The following principles are meant to complement and expand upon the basic principles of GRP and are based on the principles presented in the PAHO/PANDRH concept note and recommendations on regulatory reliance principles (5).

a) Universality

Reliance applies to all NRAs irrespective of their levels of maturity or resources. Lack of resources or capacity are not the exclusive drivers for reliance. Indeed, reliance is relevant for all resource settings, representing an increasingly important mechanism for improving regulatory efficiency and effectiveness.

b) Sovereignty of decision-making

The decision to practise reliance, and how best to implement reliance, rests with the country. Reliance does not imply dependence. In applying reliance in their daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.
c) **Transparency**

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent regarding the standards, processes and approaches adopted in implementing reliance measures. In addition, the basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties.

Furthermore, it is incumbent upon NRAs to practise transparency in regulatory operations and decisions, not only as a fundamental principle of GRP and “open government”, but also towards building trust and maximizing opportunities for cooperation and reliance as part of a shared regulatory community responsibility. In other words, regulatory authorities are an increasingly important audience and beneficiaries of measures that promote transparency in regulation through the publishing and sharing of regulatory information.

d) **Respect of national and regional legal basis**

Reliance practices should be coherent with national and regional legal frameworks and medical products’ policy and supported by clear mandates and regulations that enable the efficient implementation of reliance as part of government policy on good regulation. The driving force behind the adoption of these legal frameworks should be the efficiencies and capacity to be gained by reliance, not the minimization of resources for regulatory functions. Where regulations giving explicit legal footing and visibility to reliance practice do not exist, reliance may still be adopted through the interpretation of existing regulations provided that the legal framework does not preclude the application of reliance approaches by the NRA. Implementing reliance can be done through policy changes as long as it is broadly consistent with the legislation. If prohibitions to apply reliance exist, they should be considered for revision.

e) **Consistency**

Reliance on a specific assessment or decision from another authority should be established for specific and well-defined categories of products and processes. The scope of regulatory activities where reliance may be practised should be clearly defined and the process for practising reliance should be transparent and predictable. Thus, it is expected that reliance shall be applied consistently for products/processes in the same predetermined categories.
f) Competency

The implementation of reliance approaches requires that NRAs have built the necessary competencies for critical decision-making. Setting up the reliance approach will normally require the involvement of senior regulatory staff and managers who are competent to make the best use of foreign information in the local context. NRAs should also maintain the appropriate scientific expertise of their staff needed for activities where they do not apply reliance, for example, such as in post-marketing surveillance activities.

Equally, authorities being relied upon should possess and maintain competencies and operate within a robust and transparent regulatory system, underpinned by international standards and practices as well as a well-functioning quality system. Competencies may be benchmarked using transparent processes to develop trust and build confidence in the reference authorities.

8. Considerations

A number of considerations can guide reliance approaches and facilitate their successful implementation. These considerations include general aspects as well as barriers that NRAs need to overcome and enablers that will help in implementing reliance approaches. The non-exhaustive list of considerations presented below will be further elaborated in the case studies, practice guides and the reliance repository.

8.1 General considerations

a) Reliance anchored in a national regulatory authority strategy

In addition to having a legal basis supporting, or at least not precluding reliance approaches (see above under “Principles underpinning good reliance practices”), the application of reliance should be anchored in the NRA’s strategy, endorsed by senior management and in the respective higher-level National Policy in order to provide a mandate, direction and expectations to NRA staff, guiding them in their day-to-day work. The strategy should be further detailed in procedures and integrated in processes to ensure that maximum benefits accrue. It should also include considerations on a sustainable funding model for the NRA when implementing reliance. The strategy should be published in order to make it accessible and understandable to external stakeholders. Additionally, the implementation of reliance should be supported by training and periodic reviews in order to ensure that standards are being maintained, to assess whether or not objectives are being met, and to make refinements where warranted.
NRAs that are practising reliance should establish and publish a list of reference regulatory authorities together with the criteria used for identifying them. In order to qualify reference regulatory authorities, an NRA may refer to an assessment performed by an independent organization (e.g. WHO Benchmarking, International Organization for Standardization (ISO) accreditation, etc.).

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance in their country and region and to share their experiences with other regulatory authorities. Where possible, specific measurement of the impact of reliance is encouraged, for example, in terms of cost savings, efficiencies in the number of products reaching markets, a redirection of scarce resources to areas of higher regulatory risks, and so on.

b) Cultural change

The implementation of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on other NRA outputs. It is essential that the benefits of the strategy be understood and supported at the operational level and that staff expected to implement reliance approaches have input into their development.

This will require effective preparation, messaging and support from management and peers that articulates the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or causing the loss of scientific and regulatory competence and capacity. In fact, the use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through networking, twinning, staff visits/staff exchanges, etc.). Furthermore, the effective use of such information within the local context requires skills, ability and experience. Thus, the skill set needed to practice reliance will need to be developed in the NRA’s workforce.

It also requires that upper management, reviewers, inspectors and other staff build confidence and trust in work that has been done by other NRAs or trusted authorities. Building trust in other NRAs’ work requires time and a change in the culture within the relying NRA. Some regulatory authorities and systems already practice reliance and that experience should be leveraged to promote acceptance and avoid pitfalls.

Trust should also be built with the public and healthcare professionals in order to inform and assure them that the use of reliance offers a more efficient and effective regulatory oversight.
c) **Flexibility in approach: “one size doesn’t fit all”**

Following the principles listed above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others as part of their routine regulatory oversight and/or during special circumstances such as public health emergencies. Reliance is a tool offering flexibility to NRAs. Whatever the approach, the NRA needs to consider its own capacities and to establish clear goals when adopting reliance.

d) **Implementing reliance needs investment**

As stated above, reliance should increase the efficiency and effectiveness of a regulatory system in a country and/or region. Nevertheless, it is important to recognize that the implementation of reliance approaches will first require time and investment. This may include but may not be limited to: legislative changes and the development of guidance documents, the development of approaches and elaboration of procedures and processes, confidence-building through parallel or joint reviews and supported by staff exchanges, the training of staff, dialogue with industry and other stakeholders, as well as the establishment of, or access to, information-sharing platforms. To the best extent possible, the use of publicly available information should also be pursued.

e) **“Sameness” of the product in different jurisdictions**

One of the most critical aspects when applying reliance is the verification of the “sameness” of the medical product in different jurisdictions. Reliance can only be applied if the NRAs have the assurance that the medical product assessed by the reference regulatory authority is the same as the one submitted to the NRA, intending to use a foreign assessment as the basis for its own assessment and regulatory decision-making. The role of the manufacturer is essential here in order to confirm the sameness of a product and to provide the same documentation to different NRAs. As part of the process, the manufacturer should confirm in the application that the product is the same and that the dossier contains the same information as much as possible, taking into consideration any potential national requirements.

When addressing the sameness of the medical product, all relevant aspects have to be considered in order to confirm that the product is the same (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same manufacturing process and site of production, etc.). Additionally, supporting safety, efficacy and quality studies, indications and conditions of use, and so on, should be the same. The impact of potential justified differences should be assessed by the manufacturer and the relying NRA in determining the merit of using foreign regulatory reports or decisions.
f) The role of industry

Industry plays a crucial role in the successful application of reliance mechanisms by NRAs. While industry is widely supportive of reliance as a concept and practice that can bring about efficiency gains, industry must also have clear guidance on its application and see meaningful benefits.

Industry’s support and stringent adherence to the factors that give validity to the reliance process is vital for filing applications in multiple countries or regions, ensuring the sameness of products submitted to reference regulatory authorities and relying NRAs, and sharing unredacted and complete information.

g) Reliance in case of a public health emergency

In case of a public health emergency, reliance approaches represent an even more essential tool and should be applied to accelerate access to medical products needed in the context of the emergency.

8.2 Barriers

a) Lack of political will

The lack of political will and support at government level can make it difficult for NRAs to implement reliance in their daily practice, even if a legal basis is established supporting (or not precluding) reliance and NRAs’ support reliance as a strategy and approach.

b) Lack of accessible information and confidentiality of information

The lack of access to assessments of reference regulatory authorities can pose a major barrier to implementing effective reliance strategies. Reference regulatory authorities should strive to make assessments and other regulatory information publicly available whenever possible.

Sensitive, non-public information included in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential, commercial, trade secret or personal information. In some circumstances, the sharing of such information may require the prior consent of the manufacturer. Given the sensitivity of such information, NRAs may require that confidentiality agreements be signed which govern the exchange, management and disclosure of such information. Such information should always be exchanged using secure channels or information-sharing platforms.
Non-public regulatory reports might also be obtained directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. In that case, manufacturers are encouraged to submit complete and unredacted reports to NRAs.

c) **Other considerations**

Additional barriers can include language, differences in country-specific regulatory requirements and evidentiary standards, the level of detail in regulatory reports and, as previously noted, internal resistance and insufficient knowledge of the reference regulatory authority and how it operates. All such factors should be considered in developing the appropriate reliance strategies, as will be further elucidated in the companion documents to follow.

### 8.3 Enablers

a) **Trust**

Trust is a critical element since the reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives that foster trust among regulatory authorities are essential to promoting reliance. Trust comes from increasing familiarity and understanding in what stands behind regulatory outputs. By sharing information, including the standards applied to regulatory decisions, working together and learning each other’s ways of working, confidence can be built which thereafter leads to the effective use of reliance in regulatory work. Trust can be built in phases, starting with reliance using the exchange of reports and moving to work-sharing or joint assessments. Regulatory authorities may also consider using applications of lower risk to initiate reliance processes.

b) **Convergence and harmonization**

Convergence and the harmonization of requirements and standards are important enablers of regulatory cooperation and reliance. The more requirements and standards are alike, the more opportunity for collaboration and reliance exists.

The differences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. The system upon which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should preferably rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines (e.g. guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), WHO guidelines).
c) **Information-sharing and dialogue between regulators**

Information-sharing is an essential part of reliance and NRAs are encouraged to share information and good practices with other NRAs as much as possible. The increasing dialogue between regulators is seen in the growing number of international initiatives such as the IPRP or the International Conference of Drug Regulatory Authorities (ICDRA), as well as regulatory information- and work-sharing networks such as PANDRH, the South-East Asia Regulatory Network (SEARN), regulatory networks in the Regional Economic Communities (RECs) under the African Medicines Regulatory Harmonisation (AMRH) Initiative or the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group (PPWG), and so on, which are great facilitators for reliance.

d) **Economic or legal integration**

In situations where there is economic or legal integration in a region or for a group of countries, reliance is facilitated and strengthened by the existing mutual provisions, such as the EU, the Eurasian Economic Union, RECs in Africa, ASEAN, the Asia-Pacific Economic Cooperation (APEC) or the Southern Common Market (MERCOSUR).

e) **Engagement of stakeholders**

All relevant stakeholders, including industry, healthcare professionals, policy makers and the public, should be engaged and/or informed in order to increase the understanding and acceptance of reliance approaches as they present some clear benefits for all parties involved. Communications and engagement with stakeholders should be tailored to the target audience.
9. Conclusions

Reliance is seen by a growing number of regulatory authorities as an important means of improving the efficiency and effectiveness of regulatory operations in the oversight of medical products. It allows NRAs to make the best use of resources, build capacity, increase the quality of regulatory decisions, reduce duplication of effort and, ultimately, promote access to safe, efficacious and quality-assured medical products. By adopting reliance measures whenever possible within a well-structured framework, underpinned by national or regional policies and strategies, regulators may focus their resources on key activities that cannot be undertaken by others and that contribute to public health.

Reliance represents a “smarter” form of regulation based on constructive regional and international collaboration, one that will also facilitate and promote convergence and the use of common international standards.

Reliance does not represent a less stringent form of regulation nor an outsourcing of regulatory mandates or a compromise to independence. On the contrary, the decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority.

The inclusion of reliance-related provisions as part of their flexible regulatory pathways is encouraged and should be considered for all regulatory functions over the medical product life cycle, as appropriate.

The principles and considerations presented in this document should be taken into consideration when implementing regulatory reliance frameworks or strategies. While reliance may be viewed as a particularly useful strategy for regulatory authorities with very limited resources and capacity, it is equally relevant for well-resourced NRAs. It is an approach to be used by all NRAs and, as such, should become an integral part of regulatory operations and regulatory lexicon.
Annex 1: Examples

Regulatory reliance can take many forms and encompasses a broad array of regulatory approaches and practices that can involve two or more regulatory authorities. In addition, it can be limited to a discrete regulatory process or function or include the full scope of regulatory functions over the entire life cycle of a medical product.

There are many examples around the world that illustrate the current use of reliance and the diverse models in which national regulatory authorities (NRAs) leverage the work done by others.

Examples are given below to illustrate the different points addressed in this document and to show the use of reliance in the different regulatory functions. The list below is not exhaustive but just an illustration of the current practices of reliance taking place globally. It may be replaced in future by a comprehensive repository of reliance approaches to be established as a part of the Good Reliance Practices (GRelP) toolbox.

a) Clinical trials

Work-sharing for clinical trial assessment is happening in some regions, such as the Voluntary Harmonisation Procedure in the European Union (8) and via the African Vaccine Regulatory Forum (AVAREF) (9). By assessing clinical trial applications together, NRAs, and in some cases ethic committees from different countries, can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the approval process across countries. The AVAREF platform has been instrumental in building the capacity of regulators and ethics committees, promoting the use of international standards and expediting clinical trial assessments and decisions for medical products of high public health interest in both emergency and normal circumstances. Towards this end, a guideline and platform for joint assessment of clinical trials applications, as well as Good Clinical Practices (GCP) site inspections, have been developed and implemented in order to facilitate product development, regulatory decision-making and access to promising new medical products.
b) Marketing authorization

Abridged regulatory pathways using reliance for initial marketing authorization

Several pathways are available through stringent regulatory authorities (SRAs) or the World Health Organization (WHO) in order to enable the use of an abridged reliance pathway. The EU Article 58, also referred to as European Union Medicines for all (EU-M4 all) (10), the Swissmedic Marketing Authorisation for Global Health Products (MAGHP) (11) procedures and the WHO Collaborative Registration Procedure (CRP) (12) are three examples of abridged regulatory pathways using reliance to facilitate the registration of medicinal products in target countries.

In addition to facilitating in-country registration, the EU Article 58 and the Swissmedic MAGHP procedures provide experts from target NRAs the opportunity to both observe and participate actively in the assessment procedures, with the aim of building their own capacities and to establish confidence in the processes.

The CRP facilitates the assessment and accelerates the national registration of WHO prequalified medical products and medicines approved by an SRA. The CRP operates by providing unredacted assessment, inspection and performance evaluation (in the case of in vitro diagnostics) reports upon request (and with the consent of the manufacturer) to participating NRAs, primarily in low- and middle-income countries. The procedures are detailed in WHO guidelines, which also include guidance on how receiving NRAs can make the most efficient use of the reports in reaching their own decisions. Participating NRAs are expected to reach a decision on authorization within 90 calendar days (regulatory time). The CRP tool has shown to be successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

Quality information

Many NRAs, as well as the WHO Prequalification Programme (WHO PQ), recognize Certificates of Suitability to the monographs of the European Pharmacopoeia (CEP) (13) for active pharmaceutical ingredients (API) as a validation of the quality of a certain API. Some countries also recognize the Confirmation of API Prequalification (CPQ) issued by the WHO PQ for APIs (14). These two examples not only provide assured mechanisms of reliance, but also reduce the documentation requirements for countries that recognize these certificates. Where a CEP or CPQ is issued, the receiving NRA does not have to duplicate the API assessment but can focus on specific sections not covered under CEP or CPQ.
Work-sharing

The Australia-Canada-Singapore-Switzerland Consortium (ACSS Consortium) (15) is a coalition which was formed in 2007 by “like-minded” medium-sized regulatory authorities in order to promote work-sharing based on greater regulatory collaboration and the alignment of regulatory requirements. The ACSS Consortium explores opportunities for information- and work-sharing initiatives in areas including biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country’s area of strength, addresses gaps in science, knowledge and expertise and leverages resources to help expedite risk assessment processes, all the while maintaining or raising quality and safety standards. The Consortium builds on existing international networks, initiatives and mechanisms in order to advance work- and information-sharing along health product life cycles.

Joint assessments

Joint assessments can provide significant benefits to NRAs by sharing the workload, building capacity by bringing broader experience and expertise to bear, and helping to build trust in one another’s assessments and decision-making processes. Similarly, industry can benefit from a common review process and set of questions in terms of both resource and time-savings as compared to interacting separately with multiple countries. In recognition of these benefits, a growing number of joint assessment initiatives have been established within the framework of regional regulatory networks, sometimes driven by the higher-level priorities of economic blocks seeking to create common markets.

Examples of joint assessments initiatives include, for example, those in the Regional Economic Communities in Africa (East African Community (EAC) (16), ZAZIBONA (17) in the Southern African Development Community (SADC), the Economic Community of West African States (ECOWAS)/West African Health Organization (WAHO) (18), as well as the Association of Southeast Asian Nations (ASEAN) Joint Assessment Coordinating Group (19), and so on.

Unilateral recognition

The Mexican Federal Commission for the Protection against Sanitary Risk (COFEPRIS) has implemented a unilateral recognition of marketing authorizations from reference regulatory authorities (20). This Agreement recognizes the requirements and procedures authorized by the reference health authorities as being equivalent for the purposes of evaluation of the marketing authorization applications for allopathic medicinal products, biological medicinal products, vaccines and blood products in Mexico.
Mutual recognition

The EU system is an example of highly integrated regulatory cooperation and its multiple regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The various routes to the approval of medicines in the EU system are based on a single assessment system so that any assessment report from any of the agencies in the EU network can be used as a basis for reliance by other regulators. In this specific case, a strong and common legal framework and harmonized regulatory standards shared among all EU countries enabled and facilitated reliance.

c) Post-authorization procedures

When an NRA has relied upon another NRA for their initial approval, similar reliance measures should be considered for post-authorization changes such as variations. In the case of CRP, for example, the participating NRAs for prequalified products are informed by WHO of any variations approved by WHO Prequalification Team.

d) Testing and lot release

Network of Official Medicines Control Laboratories

The Network of Official Medicines Control Laboratories (OMCLs) support regulatory authorities in controlling the quality of medicinal products available on the market. Collaboration within the Council of Europe’s General European OMCL Network (GEON) (21) makes the best use of resources via resource pooling and avoids duplication of work or testing. Some of the main goals of the Network are to set mutual recognition, within the members of the networks, of tests carried out by OMCLs at the national level, coordinate activities among the OMCLs, and facilitate knowledge and work-sharing.
Lot release and quality monitoring of vaccines and other biotherapeutic products

Launched in 2017, the WHO-National Control Laboratory Network for Biologicals (WHO-NNB) (22) brings together National Control Laboratories (NCLs) and NRAs of vaccine-producing and vaccine-recipient countries, WHO contract laboratories, manufacturer associations, WHO Regional Offices and other stakeholders, including donors. The Network works towards the effective use of globally available resources in providing a platform and infrastructure for the exchange of quality and technical information. The main objective of the Network is to facilitate the access to and availability of prequalified vaccines (or other biotherapeutic products) through reliance on the batch release of the respective Network member NRAs/NCLs by recipient countries, thereby reducing redundant testing and contributing to more cost-effective testing and more effective regulatory oversight.

e) Pharmacovigilance

In the field of pharmacovigilance, the exchange and sharing of data is critical. More than 100 Member States contribute by sharing their safety data to the WHO Global database of individual case safety reports (ICSR) - VigiBase - developed and maintained by the Uppsala Monitoring Center (UMC) (23). Member States rely upon this resource (and thereby, on each-others’ data) as a single point of pharmacovigilance information, to confirm and validate signals of adverse events with medicines and vaccines that they may have observed within their own jurisdictions.

f) Inspections

In the field of inspections, governments and NRAs in different regions and parts of the world have worked on mutual recognition agreements in order to rely on each other’s inspection outcomes, avoiding the duplication of inspections and making the best use of resources (e.g. EU Mutual Recognition Agreements (24) with Australia, Canada, Japan, Switzerland and the United States of America (USA); ASEAN Mutual Recognition Agreement (25), etc.).

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) (26) is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. It aims at facilitating cooperation and networking between competent authorities, regional and international organisations, thus increasing mutual confidence regarding GMP inspections.
Reliance is also an important aspect for conducting desktop assessment of compliance with relevant good practice guidelines and requirements, as described in the respective WHO guidance (27).

g) **Examples in the field of medical devices**

The use of reliance is equally prevalent in the regulation of medical devices. An example of this is the Medical Device Single Audit Program (MDSAP) (28) originally developed through the auspices of the International Medical Device Regulators Forum (IMDRF). Under this program, the regulatory authorities of Australia, Brazil, Canada, Japan and the USA have pooled their resources in order to develop and implement a robust system of oversight of third party auditing organizations that, in turn, conduct audits of the quality management systems of medical device manufacturers. The MDSAP allows an auditing organization recognized by the Program to conduct a single regulatory audit that satisfies the relevant requirements of the regulatory authorities participating in the program. Collective regulatory resources are directed at establishing and maintaining the oversight of auditing organizations, providing a more effective use of limited regulatory resources. Employing a single audit program allows regulatory authorities to efficiently leverage resources and streamline the regulatory process without compromising public health and to promote more aligned and consistent regulatory requirements.

**Vigilance**

The IMDRF has also set guidance for the exchange of information between national competent authorities with respect to medical device safety (29). The system focuses on incidents that represent a serious public health threat that goes beyond borders in order to inform other NRAs of such.
References


18. ZAZIBONA. Southern African Development Community (http://www.zazibona.com/).


27. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (https://www.picscheme.org/).


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Guideline on data integrity

DRAFT FOR COMMENTS

Please send your comments to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 15 August 2020.

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

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Guideline on data integrity

1. Introduction and background

1.1. Data governance and its related measures are important to ensure the reliability of data and records in good practice (GxP) activities and regulatory submissions. The data and records should be attributable, legible, contemporaneous, original and accurate, commonly referred to as “ALCOA+”.

1.2. In recent years, the number of observations made regarding the integrity of data, documentation and record management practices during inspections of good manufacturing practice (GMP) (2), good clinical practice (GCP) and good laboratory practice (GLP) have been increasing. The possible causes for this may include (i) reliance on inadequate human practices; (ii) poorly defined procedures; (iii) resource constraints; (iv) the use of computerized systems that are not capable to meet regulatory requirements or are inappropriately managed and validated (3,4); (v) inappropriate data flow (e.g. manual data transfer); and (vi) failure to adequately review and manage original data and records.

1.3. Data governance control strategies using quality risk management principles (5) are required to mitigate such risks. Examples of controls may include, but are not limited to:

- the establishment and implementation of a data integrity (DI) policy;
- the establishment and implementation of procedures that will facilitate compliance with DI requirements and expectations;
- the adoption of a quality culture within the company that encourages personnel to be transparent about failures, which includes a reporting mechanism inclusive of investigation and follow-up processes;
- the application of quality risk management (QRM) with the identification of all areas of risk to DI through data integrity risk assessment (DIRA) and the implementation of appropriate controls to eliminate or reduce risks to an acceptable level throughout the life-cycle of the data;
- ensuring sufficient resources are available to implement and complete a DI program and to monitor compliance with DI policies and procedures and processes, and to facilitate continuous improvement of both;
- the provision of necessary training for personnel in, for example, GxP, computerized systems and the principles of DI;
the implementation and validation of computerized systems appropriate for their intended use, including all relevant DI requirements in order to ensure that the computerized system has the necessary controls to protect the electronic data (3);

- the definition and management of the appropriate roles and responsibilities for contract givers and contract acceptors, entered into quality agreements and contracts including a focus on DI requirements.

2. Scope

2.1. This guideline provides information, guidance and recommendations to facilitate compliance with regulatory requirements related to DI documentation and record management.

2.2. The scope of this guideline is designated as "GxP" for pharmaceutical products. The principles could also be applicable to vector control products.

2.3. Where possible, this guideline has been harmonised with other published documents. This guideline should also be read with other WHO good practices guidelines and publications.

2.4. The principles of this guideline apply to contract givers and contract acceptors. Contract givers are ultimately responsible for the integrity of data provided to them by contract acceptors. Contract givers should therefore ensure that contract acceptors have the appropriate capabilities and comply with the principles contained in this guideline documented in quality agreements.
3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

**ALCOA+.** A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” which puts additional emphasis on the attributes of being complete, consistent, enduring and available throughout the data life cycle for the defined retention period – implicit basic ALCOA principles.

**archiving.** Archiving is the process of protecting records from the possibility of being further altered or deleted, and storing these records under the control of independent data management personnel throughout the required retention period. Archived records should include, for example, associated metadata and electronic signatures.

**audit trail.** The audit trail is a form of metadata containing information associated with actions that relate to the creation, modification or deletion of GxP records. An audit trail provides for a secure recording of life cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the “who, what, when and why” of the action.

**certified true copy or true copy.** A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

**data.** All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data which are generated or recorded at the time of the GMP activity and which allow full and complete reconstruction and evaluation of the GMP activity.

Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio or video files or any other media whereby information related to GMP activities is recorded.
**data governance.** The sum total of arrangements which provide assurance of data quality. These arrangements ensure that data, irrespective of the process, format or technology in which it is generated, recorded, processed, retained, retrieved and used will ensure an attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available record throughout the data life cycle.

**data life cycle.** All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored, until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data, in a manner commensurate with the potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life cycle.

**electronic signatures.** A signature in digital form (bio-metric or non-biometric) that represents the signatory. In legal terms, it is the equivalent of the handwritten signature of the signatory.

**good practices (GxP).** An acronym for the group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as GLP, GCP, GMP, good pharmacovigilance practices (GVP) and good distribution practices (GDP).

**metadata.** Metadata are data about data that provide the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in weighing, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, and so on. Other examples of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

**raw data.** The original record (data) which can be described as the first-capture of information, whether recorded on paper or electronically. Raw data is synonymous with source data).
4. **Data governance**

4.1. Senior management is responsible for the establishment, implementation and control of an effective quality system and a data governance system by assuring that policies, training and technical systems are in place.

4.2. Senior management is responsible for providing the environment to establish, maintain and continually improve the quality culture, supporting the transparent and open reporting of deviations, errors or omissions at all levels of the organization.

4.3. Senior management should be accountable for the implementation of systems and procedures in order to minimise the potential risk to DI, and to identify the residual risk using risk management techniques such as the principles of the guidance on quality risk management from WHO (5) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (6).

4.4. There should be a written DI policy.

4.5. Data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available. This is generally referred to as ALCOA+.

4.6. The quality system, including documentation such as procedures and formats for recording data, should be appropriately designed and implemented in order to provide assurance that records and data meet the principles contained in this guideline.

4.7. Data governance should address the data roles, responsibilities and accountability throughout the life cycle and consider the design, operation and monitoring of processes/systems to comply with the principles of DI, including control over intentional and unintentional changes to data.

4.8. Data governance systems should include e.g.:
   - training in the importance of DI principles;
   - the creation of an appropriate working environment;
   - active encouragement of collecting feedback and continuous improvement; and
   - the reporting of errors, unauthorized changes, omissions and undesirable results.
4.9. The data governance programme should include policies and procedures addressing data management. Elements of effective management governance should at least include:

- management oversight and commitment;
- the application of QRM;
- quality metrics and performance indicators;
- validation;
- change, incident and deviation management;
- security, cybersecurity, access and configuration control;
- database build, data collection, data review, blinded data, randomization;
- the tracking, trending, reporting of DI anomalies, and lapses or failures for further action;
- the prevention of commercial, political, financial and other organizational pressures;
- adequate resources, systems;
- workload and facilities to facilitate the right environment that supports DI and effective controls;
- monitoring;
- record-keeping;
- training; and
- awareness of the importance of DI, product quality and patient safety.

4.10. There should be a system for the regular review of documents and data for consistency with ALCOA+ principles. This includes paper records and electronic records in day-to-day work, system and facility audits and self-inspections.

4.11. The effort and resources applied to assure the integrity of the data should be commensurate with the risk and impact of a DI failure.

4.12. Where DI weaknesses are identified, the appropriate corrective and preventive actions (CAPA) should be implemented across all relevant activities and systems and not in isolation.

4.13. Significant DI lapses identified that may impact patient safety, product quality or efficacy, should be reported to the relevant medicine regulatory authorities.
4.14. Changing from automated or computerised systems to paper-based manual systems or vice-versa will not in itself remove the need for appropriate DI controls.

4.15. Good documentation practices should be followed in order to ensure that all records are complete and in accordance with ALCOA+ principles.

4.16. Records (paper and electronic) should be kept in a manner that ensures compliance with the principles of this guideline. These include but are not limited to:

- restricting the ability to change dates and times for recording events;
- using controlled documents and forms for recording GxP data;
- controlling the issuance of blank paper templates for data recording of GxP activities, with reconciliation and authenticity controls where required;
- defining access and privilege rights to automated systems, ensuring segregation of duties;
- enabling audit trails and restricting the ability to enable or disenable audit trails;
- having automated data capture systems and printers connected to equipment and instruments in production and quality control where possible;
- ensuring the proximity of printers to sites of relevant activities;
- design processes in a way to avoid the unnecessary transcription of data or unnecessary conversion from paper to electronic and vice versa; and
- ensuring access to original electronic data and metadata for personnel responsible for reviewing and checking data.

4.17. Systems, procedures and methodology used to record and store data should be periodically reviewed for effectiveness and updated, as necessary, in relation to new technology.

5. Quality risk management

5.1. The DIRA should be documented. This should cover systems and processes that produce data or, where data are obtained, data criticality and inherent risks.

5.2. The risk assessment should evaluate, for example, the relevant GxP computerised systems, supporting personnel, training, quality systems and extent of outsourced activities.
5.3. DI risks should be assessed, mitigated, communicated and reviewed throughout the document and data life cycle at a frequency based on the risk level, as determined by the risk assessment process.

5.4. Where the DIRA has highlighted areas for remediation, the prioritisation of actions (including the acceptance of an appropriate level of residual risk) and the prioritisation of controls should be documented and communicated. Where long-term remediation actions are identified, risk-reducing short-term measures should be implemented in order to provide acceptable data governance in the interim.

5.5. Controls identified may include organizational, procedural and technical controls such as procedures, processes, equipment, instruments and other systems in order to both prevent and detect situations that may impact on DI. Examples include the appropriate content and design of procedures, formats for recording, access control, the use of computerized systems and other means.

5.6. Controls should cover risks to data. Risks to data manipulation include deletion of, changes to, and exclusion of data or results from data sets without written justification, authorisation where appropriate, and detection.

5.7. In line with the current approach in GxP, this guideline recommends a documented risk-based approach over the life cycle of data considering data criticality. DIRA should be carried out in order to identify and assess areas of risk.

5.8. Efficient risk-based controls and the review of data and documents should be identified and implemented. The effectiveness of the controls should be verified.

6. Management review

6.1. There should be management oversight of quality metrics relevant to data governance.

6.2. Management should ensure that computerized systems are meeting regulatory requirements in order to ensure DI compliance and to avoid the acquisition of inadequate systems and software.
6.3. The effectiveness of the controls implemented should be measured against the quality metrics and performance indicators. These should include, for example:
   • the tracking and trending of data;
   • A review of audit trails in, for example, production, quality control, GLP, case report forms and data processing; and
   • routine audits and/or self-inspections, including DI and computerized systems.

7. Outsourcing

7.1. The outsourcing of activities and responsibilities of each party (contract giver and contract accepter) should be clearly described in written agreements. Specific attention should be given to ensuring compliance with DI requirements.

7.2. Compliance with the principles and responsibilities should be verified during periodic site audits. This should include the review of procedures and data (including raw data and metadata, paper records, electronic data, audit trails and other related data) held by the contracted organization that are relevant to the contract giver’s product or services.

7.3. Where data and document retention are contracted to a third party, particular attention should be paid to understanding the transfer, storage and restoration of data held under that agreement, as well as controls to ensure the integrity of data over their life cycle. This includes data in motion and data at rest. Tools should be identified to ensure data integrity, for example, encryption.

7.4. No activity, including outsourcing of databases, should be sub-contracted to a third party without the prior approval of the contract giver. This should be stated in the contractual agreements where appropriate.

7.5. All contracted parties should be aware of the requirements relating to data governance, DI and data management.
8. **Training**

8.1. All personnel who interact with GxP data and who perform GxP activities should be trained in relevant DI principles and abide by organization policies and procedures. This should include understanding the potential consequences in cases of non-compliance.

8.2. Personnel should agree to abide by DI principles and should be made aware of the potential consequences in cases of non-compliance.

8.3. Personnel should be trained in good documentation practices and measures to prevent and detect DI issues. Specific training may be required in cases where computerized systems are used in the generation, processing, interpretation and reporting of data and where risk assessment has shown that this may be required. Such training should include, for example, evaluating the system security, back-up, configuration settings and reviewing of electronic data and metadata, such as audit trails and logs, for individual computerized systems used in the generation, processing and reporting of data.

9. **Data and data transfer**

9.1. Data may be recorded manually reflecting an observation, result or other data and information on paper, or electronically by using equipment and instruments including those linked to computerised systems. A combination of manual and electronic systems may also be used, referred to as a “hybrid system”.

9.2. The same considerations for DI apply to data sets such as photographs, videos, DVDs, imagery and chromatography plates. There should be a documented rationale for the selection of such a method.

9.3. Risk-reducing supervisory measures should be implemented where there is difficulty in accurately and contemporaneously recording data related to critical process parameters or critical quality attributes.

9.4. Results and data sets require independent verification if deemed necessary from the DIRA or by another requirement.
9.5. Programmes and methods (such as acquisition and processing methods) should ensure that data meet ALCOA+ principles. Where results or data are processed using a different method/parameters, then the acquisition method should be recorded. Audit trails with the required details should allow for reconstruction of all data processing and administrative activities.

9.6. Data transfer should not result in any changes to the content or meaning of the data. The transfer should be tracked in the audit trail or by other suitable means.

9.7. Data transfer should be validated and computerized interfaces tested, especially systems which map and or transform data moving between computerized systems.

10. Good documentation practices

10.1. The principles contained in this section are applicable to paper data.

10.2. Data and recorded media should be durable. Ink should be indelible. Temperature-sensitive or photosensitive inks and other erasable inks should not be used, or other means should be identified in order to ensure traceability of the data over their life cycle.

10.3. Paper should not be temperature-sensitive, photosensitive or easily oxidizable. If this is not feasible or limited, then true or certified copies should be available.

10.4. Specific controls should be implemented in order to ensure the integrity of data and results recorded on paper records. These may include, but are not limited to:
   - control over the issuance and use of loose paper sheets at the time of recording data;
   - the use of permanent, indelible ink;
   - no use of pencil or erasers;
   - the use of single-line cross-outs to record changes with the identifiable person who made the change, date and reason recorded (i.e. the paper equivalent to an electronic audit trail);
   - no use of correction fluid or otherwise, obscuring the original record;
   - controlled issuance of bound, paginated notebooks;
   - controlled issuance of sequentially numbered copies of blank forms with authenticity controls; and
   - archival of records by designated personnel in secure and controlled archives.
11. **Computerized systems**

(Note. This section highlights some specific aspects relating to the use of computerized systems. It is not intended to repeat the information presented in the other WHO guidelines here, such as the WHO Guideline on computerized systems (3), WHO Guideline on validation(2) and WHO Guideline on good chromatography practices (7). See references.)

11.1. The computerized system selected should be suitable and validated for its intended use.

11.2. Where GxP systems are used to acquire, record, transfer, store or process data, management should have appropriate knowledge of the risks that the system and users may pose to the integrity of the data.

11.3. Suitably configured and validated, software should be used where instruments and equipment with computerised systems are used. The validation should cover the design, implementation and maintenance of controls in order to ensure the integrity of data. The potential for unauthorized and adverse manipulation of data during the life cycle of the data should be mitigated and, where possible, eliminated.

11.4. Where electronic systems with no configurable software and no electronic data retention (e.g. pH meters, balances and thermometers) are used, controls should be put in place in order to prevent the adverse manipulation of data and to repeat testing to achieve the desired result.

11.5. The appropriate controls of detection for lapses in DI principles should be in place. Technical controls should be used whenever possible. Additional controls should be implemented where stand-alone systems with a user-configurable output is used, for example, Fourier-transform infrared spectroscopy (FTIR) and UV spectrophotometers. Examples of detection and prevention mechanisms may include, but are not limited to, instrument usage logbooks, electronic audit trails, and external software to lockdown the personal computer workstation.

11.6. Critical records or data, including metadata, should be reviewed and retained according to risk assessment. Reduced effort and/or frequency should be justified.
Access and privileges

11.7. There should be a documented system in place that defines the access and privileges of users of computerized systems. There should be no discrepancy between paper records and electronic records, including the creation and inactivation of users.

11.8. Access and privileges should be in accordance with the role and responsibility of the individual with the appropriate controls to ensure DI (e.g. no modification, deletion or creation of data outside the allocated responsibility).

11.9. A limited number of personnel, with no conflict of interest in data, should be appointed as system administrators. Certain privileges such as data deletion, database amendment or system configuration changes should not be assigned to administrators without justification - and such activities should only be done with documented evidence of authorization by another responsible person. Records should be maintained and audit trails should be enabled in order to track activities of system administrators. Minimally, activity logging for such accounts and the review of logs by designated roles should be conducted in order to ensure appropriate oversight.

11.10. For systems generating, amending or storing GxP data, shared logins or generic user access should not be used. The computerised system design should support individual user access. Where a computerised system supports only a single user login or limited numbers of user logins and no suitable alternative computerised system is available, equivalent control should be provided by third-party software or a paper-based method that provides traceability (with version control). The suitability of alternative systems should be justified and documented (8).

Audit trail

11.11. GxP systems should provide for the retention of audit trails. Audit trails should reflect, for example, users, dates, times, original data and results, changes and reasons for changes.

11.12. All audit trails should be enabled when software is installed and remain enabled at all times. There should be evidence of enabling the audit trail. There should be periodical verification that the audit trail remained enabled throughout the data life cycle.
11.13. Where a system cannot support ALCOA+ principles by design (e.g. legacy systems with no audit trail), mitigation measures should be taken for defined temporary periods. For example, add-on software or paper based controls may be used. The suitability of alternative systems should be justified and documented. This should be addressed within defined timelines.

11.14. Routine data review should include a review of audit trails. Evidence of the reviews should be maintained.

Electronic signatures

11.15. Each electronic signature should be appropriately controlled. An electronic signature should be:
   • validated;
   • attributable to an individual;
   • free from alteration and manipulation; and
   • date- and time-stamped, where appropriate.

11.16. An inserted image of a signature or a footnote indicating that the document has been electronically signed is not adequate unless it was created as part of the validated electronic signature process. The metadata associated with the signature should be retained.

Data review and approval

11.17. There should be a documented procedure for the routine and periodic review, as well as the approval of data.

11.18. A procedure should describe the actions to be taken where errors, discrepancies or omissions are identified in order to ensure that the appropriate corrective and preventive actions are taken.

11.19. A conclusion following the review of original data, metadata and audit trail records should be documented, signed and dated.
Data backup, retention and restoration

11.20. Data should be retained in such a manner that they are protected, enduring, readily retrievable and remain readable throughout the records retention period. True copies of original records may be retained in place of the original record, where justified. Electronic data should be backed up according to written procedures.

11.21. Data and records should be kept in a secure area which provides appropriate protection. Access should be controlled.

11.22. Retention periods should be defined in authorized procedures.

11.23. Records reflecting documented reasons for the destruction of data should be maintained.

11.24. Backup and restoration processes should be validated. The backup should be done and periodically restored and verified for completeness and accuracy of data and metadata. Where any discrepancies are identified, they should be investigated.

12. Corrective and preventive actions

12.1. Where organizations use computerized systems (e.g. for GxP data acquisition, processing, interpretation, reporting) which do not meet current GxP requirements, a workplan towards upgrading such systems should be documented and implemented in order to ensure compliance with current GxP.

12.2. When GxP lapses in DI are identified, a risk-based approach may be used to determine the scope of the investigation, root cause, impact and CAPA, as appropriate. Health authorities, contract givers and other relevant organizations should be notified if the investigation identifies a significant impact or risk to, for example, materials, products, patients, reported information or data in application dossiers, and clinical trials.
References


Further reading


- Data integrity management system for pharmaceutical laboratories PDA Technical Report, No. 80; August 2018.
Annex 1. Examples in data integrity management

This Annex reflects on some examples in data integrity (DI) management in order to support the main text on DI. It should be noted that these are examples and are intended for the purpose of clarification only.

Example 1: Quality risk management and data integrity risk assessment

Risk management is an important part of good manufacturing practices (GMP). Risks should be identified and assessed and controls identified and implemented in order to assist manufacturers in preventing possible DI lapses.

As an example, a Failure Mode and Effects Analysis (FMEA) model (or any other tool) can be used to identify and assess the risks relating to any system where data are, for example, acquired, processed, recorded, saved and archived. The risk assessment can be done as a prospective exercise or retrospective exercise. Corrective and preventive action (CAPA) should be identified, implemented and assessed for its effectiveness.

For example, if during the weighing of a sample, the entry of the date was not contemporaneously recorded on the worksheet but the date is available on the print-out from a weighing balance and log book for the balance for that particular activity. The fact that the date was not recorded on the worksheet may be considered a lapse in data integrity expectations. When assessing the risk relating to the lack of the date in the data, the risk may be considered different (lower) in this case as opposed to a situation when there is no other means of traceability for the activity (e.g. no print-out from the balance). When assessing the risk relating to the lapse in DI, the severity could be classified as “low” (the data is available on the print-out); it does not happen on a regular basis (occurrence is “low”), and it could easily be detected by the reviewer (detection is “high”) – therefore the overall risk factor may be considered low. The root cause as to why the record was not made in the analytical report at the time of weighing should still be identified and the appropriate action taken to prevent this from happening again.
Example 2: Good documentation practices in data integrity

Documentation should be managed with care. These should be appropriately designed in order to assist in eliminating erroneous entries, manipulation and human error.

Formats

Design formats to enable personnel to record or enter the correct information at the right time. Provision should be made for entries such as, but not limited to, dates, time (start, finish, where appropriate), signatures, initials, results, batch numbers and equipment identification numbers. The system should prompt the personnel to make the entries at the appropriate step.

Blank forms

The use of blank forms should not be encouraged. Where blank forms are used (e.g. to supplement worksheets, laboratory notebooks and master production and control records), the appropriate controls have to be in place and may include, for example, a numbered set of blank forms issued which are reconciled upon completion. Similarly, bound paginated notebooks, stamped or formally issued by a designated personnel, allow for the detection of unofficial notebooks and any gaps in notebook pages. Authorization may include two or three signatures with dates, for example, “prepared by” or “entered by”, “reviewed by” and “approved by”.

Error in recording data

Care should be taken when entries of data and results (electronic and paper records) are made. Entries should be made in compliance with good documentation practices. Where incorrect information had been recorded, this may be corrected provided that the reason for the error is documented, the original entry remains readable and the correction is signed and dated.
Example 3: Data entry

Data entry includes examples such as sample receiving registration, sample analysis result recording, logbook entries, registers, batch manufacturing record entries and information in case report forms. The recording of source data on paper records should be in indelible ink and free from errors. Direct entry into electronic records should be done by responsible and appropriately trained individuals. Entries should be traceable to an individual (in electronic records, thus having an individual user access) and traceable to the date (and time, where relevant). Where appropriate, the entry should be verified by a second person or entered through technical means such as the scanning of bar-codes, where possible, for the intended use of these data. Additional controls may include the locking of critical data entries after the data are verified and a review of audit trails for critical data to detect if they have been altered. The manual entry of data into a computerized system should be traceable to the paper records used.

Example 4: Dataset

All data should be included in the dataset unless there is a documented, justifiable, scientific explanation and procedure for the exclusion of any result or data. Whenever out of specification or out of trend or atypical results are obtained, they should be investigated in accordance with written procedures. This includes investigating and determining CAPA for invalid runs, failures, repeats and other atypical data. The review of original electronic data should include checks of all locations where data may have been stored, including locations where voided, deleted, invalid or rejected data may have been stored. Data and metadata should not be found in other electronic folders or in other operating system logs. Electronic data should be archived in accordance with a standard operating procedure. It is important to ensure that associated metadata are archived with the relevant data set or securely traceable to the data set through relevant documentation. It should be possible to successfully retrieve data and datasets from the archives. This includes metadata. This should be done in accordance with a procedure and verified at defined intervals.

Example 5: Legible and enduring

Data and metadata should be readable during the life cycle of the data. Risks include the fading of microfilm records, the decreasing readability of the coatings of optical media such as compact disks (CDs) and digital versatile/video disks (DVDs), and the fact that these media may become brittle. Similarly, historical data stored on magnetic media will also become unreadable over time as a result of deterioration. Data and records should be stored in an appropriate manner, under the appropriate conditions.
Example 6: Attributable

Data should be attributable, thus being traceable to an individual. In paper records, this could be done through the use of initials, full handwritten signature or a controlled personal seal. In electronic records, this could be done through the use of unique user logons that link the user to actions that create, modify or delete data; or unique electronic signatures which can be either biometric or non-biometric. An audit trail that captures user identification (ID), date and time stamps and the electronic signature must be securely and permanently linked to the signed record.

Example 7: Contemporaneous

Personnel should record data and information at the time these are generated and acquired. For example, when a sample is weighed or prepared, the weight of the sample (date, time, name of the person, balance identification number) should be recorded at that time and not before or at a later stage. In the case of electronic data, these should be automatically date- and time-stamped. The use of hybrid systems is discouraged but where legacy systems are awaiting replacement, upgrade or connection to upper level systems, documented mitigating controls should be in place. (The replacement of hybrid systems should be a priority with a documented CAPA plan.) The use of a scribe to record an activity on behalf of another operator should be considered only on an exceptional basis and should only take place where, for example, the act of recording places the product or activity at risk, such as, documenting line interventions by aseptic area operators. It needs to be clearly documented when a scribe has been applied.

“In these situations, the recording by the second person should be contemporaneous with the task being performed, and the records should identify both the person performing the task and the person completing the record. The person performing the task should countersign the record wherever possible, although it is accepted that this countersigning step will be retrospective. The process for supervisory (scribe) documentation completion should be described in an approved procedure that specifies the activities to which the process applies.” (Extract taken from the Medicines & Healthcare Products Regulatory Agency (MHRA) GxP data integrity guidance and definitions (10).)
Example 8: Changes

When changes are made to any result or data, the change should be traceable to the person who made the change and the date, time and reason for the change. In electronic systems, this traceability should be documented via computer generated audit trails or in other metadata fields or system features that meet these requirements. Where an existing computerized system lacks computer-generated audit trails, personnel may use alternative means such as procedurally controlled use of log-books, change control, record version control or other combinations of paper and electronic records to meet GxP regulatory expectations for traceability to document the what, who, when and why of an action.

Example 9: Original

Original data include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GxP activity (see the definition of raw data). In some cases, the electronic data (electronic chromatogram acquired through high-performance liquid chromatography (HPLC)) may be the original data and, in other cases, the recording of the temperature on a log sheet in a room - by reading the value on a data logger – may be considered the original data. Original data should be reviewed according to the criticality and risk assessment. Proof of review should be presented (e.g. as a signature (reviewed by:) and date of the review). For electronic records, this is typically signified by electronically signing the electronic data set that has been reviewed and approved. Written procedures for data review should clarify the meaning of the review and approval signatures in order to ensure that the personnel concerned understand their responsibility as reviewers and approvers to assure the integrity, accuracy, consistency and compliance with established standards of the electronic data and metadata subject to review and approval. Written procedures for data review should define the frequency, roles and responsibilities and approach to review of meaningful metadata, such as audit trails. These procedures should also describe how aberrant data are to be handled if found during the review. Personnel who conduct such reviews should have adequate and appropriate training in the review process as well as in the software systems containing the data subject to review.
Example 10: Controls

Based on the outcome of the data integrity risk assessment (DIRA) (which should cover all areas of data governance and data management), the appropriate and effective controls should be identified and implemented in order to assure that all data, whether in paper records or electronic records, will meet ALCOA+ principles. Examples of controls may include, but are not limited to:

- the qualification, calibration and maintenance of equipment, such as balances and pH meters, that generate printouts;
- the validation of computerized systems that acquire, process, generate, maintain, distribute or archive electronic records;
- the validation of systems in order to ensure that the integrity of data will remain while transmitting between/among computerized systems;
- the validation of analytical procedures;
- the validation of production processes;
- a review of GxP records; and
- the investigation of deviations, out of trend and out of specifications results.

Points to consider for assuring accurate GxP records:

- the entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an additional check on the accuracy of the data entered manually. This check may be done by independent verification and release for use by a second authorized person or by validated electronic means. For example, to detect and manage risks associated with critical data, procedures would require verification by a second person;
- formulae for calculations entered into spreadsheets;
- master data entered into the laboratory information management system (LIMS) such as fields for specification ranges used to flag out of specification values on the certificate of analysis;
- other critical master data, as appropriate. Once verified, these critical data fields should normally be locked in order to prevent further modification and only be modified through a formal change control process;
- the process of data transfer between systems should be validated;
- the migration of data including planned testing, control and validation; and
- when the activity is time-critical, printed records should display the date and time stamp.

***
ATC/DDD Classification (Temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in April 2020.

Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 September 2020. If no objections are received before this date, the new ATC codes, DDDs and alterations will be considered final and included in the January 2021 version of the ATC/DDD Index.

New ATC 5th level codes:

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1: Alteration of 4th level name to C10BA *Combinations of various lipid modifying agents*
2: New ATC 4th level J05AJ *Integrase inhibitors* valid from January 2021

**New ATC level codes (other than 5th levels):**

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<td>Cyclin-dependent kinases (CDK) inhibitors</td>
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<td>Hedgehog pathway inhibitors</td>
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### ATC level name

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### Change of ATC level codes:

Alterations as a consequence of new ATC 3rd and 4th levels to be implemented in the ATC Index 2021: J05AJ Integrase inhibitors, L01CE Topoisomerase 1 inhibitors, L01E Protein kinase inhibitors with 4th levels, and 4th levels in L01X Other antineoplastic agents, see list of new ATC level codes (other than 5th levels), see above:

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Change of ATC level names:

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<td>Combinations of various lipid modifying agents</td>
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<td>HMG CoA reductase inhibitors, other combinations</td>
<td>Lipid modifying agents in combination with other drugs</td>
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1: Fe\(^3+\)  
2: expressed as ravuconazole  
3: refers to imipenem  
4: refers to meropenem  
5: expressed as trientine

WHO Collaborating Centre for Drug Statistics Methodology  
Oslo, May 2020
**ATC/DDD Classification (Final)**

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2019.

These are considered as final and will be included in the **January 2021 version of the ATC/DDD Index.**

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<td>zinc sulfate</td>
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1) Oral formulations only indicated in treatment of renal secondary hyperparathyroidism
2) Oral formulations only indicated in treatment of Cushing’s syndrome

**New ATC level codes (other than 5th levels):**

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<tr>
<th>ATC level name name</th>
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<td>Other antiparkinson drugs</td>
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**New DDDs:**

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<th>unit</th>
<th>Adm.R</th>
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WHO Collaborating Centre for Drug Statistics Methodology
Oslo, May 2020

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