NOTICE TO STAKEHOLDERS

FREQUENTLY ASKED QUESTIONS BY THE MANUFACTURING, TRIAL AND TESTING ORGANIZATIONS IN CONNECTION WITH SOME OF THEIR CONSTRAINTS FACED DURING THE COVID-19 OUTBREAK

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INTRODUCTION AND BACKGROUND

On 30 January 2020, WHO Director-General, Dr Tedros Ghebreyesus declared that the outbreak of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) had constituted a Public Health Emergency of International Concern. Since then many countries have implemented measures to combat the spread of the disease, including but not limited to travel restrictions lockdown, quarantine and social distancing.

As a result, manufacturers of active pharmaceutical ingredients (APIs), finished pharmaceutical products (FPPs), vaccines, medical devices including in-vitro diagnostics (IVDs), vector control products, quality control laboratories and contract research organizations (CROs) of WHO Prequalified Products are facing several challenges during this COVID-19 pandemic. In particular, some of them may be unable to fully meet their usual responsibilities of following Good Manufacturing Practices (GMP), Good Practice for Quality Control Laboratories (GPPQCL), Good Practice for Pharmaceutical Microbiology Laboratories (GPPML) Good Clinical Practices (GCP), Good Laboratory Practices (GLP) and Quality Management System (QMS) requirements respectively.

This document was developed by WHO Prequalification Unit - Inspection Team (PQT/INS) with input from the Norms and Standards Pharmaceuticals (NSP), Health Products Policy and Standards Department, WHO. It provides basic guidance to manufacturers/laboratories/contract research organizations (herein after referred to as organizations), on regulatory expectations and flexibility during the COVID-19 pandemic in the form of questions and answers. It is underlined that the pandemic is affecting countries at different levels and the progress of the pandemic in each country may be at different stage; hence national measures and guidance should also be considered. The definitive aim is to ensure the quality, safety, efficacy and continuity in the supply of products and services in order to attain a high level of public health. The document will be updated to address new questions and to include further information for organizations to the evolution of the pandemic. It will remain valid until further notice.

1. QUESTIONS RELATED TO INSPECTIONS

1.1 Would WHO PQT/INS consider waiving or postponing a routine site inspection for manufacturing, trial and testing organizations which have been inspected by WHO PQT/INS?

Yes, WHO PQT/INS may consider waiving or postponing an onsite inspection based on an initial risk assessment provided a successful WHO PQ inspection was performed in the past. In lieu of an onsite inspection, WHO may consider carrying out a desk assessment. The organizations would be contacted by WHO PQT/INS and requested to provide further information, where necessary. WHO PQT/INS will inform the organizations on the compliance outcome. If the desk assessment cannot adequately fulfil the purpose and requirement of the inspection, an onsite inspection will need to be performed when travel restrictions are lifted.

1.2. Would WHO PQT/INS consider "waiving an onsite inspection", for new products under prequalification, of organizations already inspected by WHO PQT/INS?

Yes, WHO PQT/INS may consider waiving an onsite inspection based on an initial risk assessment provided a successful WHO PQ inspection has been performed. In lieu of an onsite inspection, WHO may consider carrying out a desk assessment. The organizations would be contacted by WHO PQT/INS and requested to provide further information, where necessary. WHO PQT/INS will inform the organization on the compliance outcome. If the desk assessment cannot adequately fulfil the purpose and requirement of the inspection, an onsite inspection will need to be performed when travel restrictions are lifted.

1.3. Would WHO PQT/INS consider waiving an onsite inspection of a new organization (addition of a new manufacturing site) for an already prequalified product?

Yes, WHO PQT/INS may consider waiving an onsite inspection based on an initial risk assessment provided a successful inspection has been performed by another regulatory body. In lieu of onsite inspections, WHO may consider carrying out a desk assessment. The organizations would be contacted by WHO PQT/INS and requested to provide further information, where necessary. WHO PQT/INS will inform the organization on compliance outcome. If the desk assessment cannot adequately fulfil the purpose and requirement of the inspection, an onsite inspection will need to be performed when travel restrictions are lifted.

1.4. Would WHO PQT/INS consider waiving an onsite inspection for a new organization relating to a new product under assessment?

Yes, WHO PQT/INS may consider waiving an onsite inspection on a case by case basis for high priority medicines, vaccines, medical devices including IVDs, vector control products and related organizations. In lieu of onsite inspections, WHO may consider carrying out a desk assessment. The organizations would be contacted by WHO PQT/INS and requested to provide further information, where necessary. WHO PQT/INS will inform the organization on the compliance outcome. If the desk assessment cannot adequately fulfil the purpose and requirement of the inspection, an onsite inspection will need to be performed when travel restrictions are lifted.

1.5. Would WHO PQT/INS consider waiving an onsite inspection of a Quality Control Laboratory (QCL)?

Although inspection of QCLs is not considered a priority during the COVID-19 pandemic, WHO PQT/INS may consider postponing the inspection on a case by case basis. In lieu of an onsite inspection, WHO may consider carrying out a desk assessment. The laboratory would be contacted by WHO PQT/INS and requested to provide further information, where necessary. WHO PQT/INS will inform the organization on the compliance outcome. If the desk assessment cannot adequately fulfil the purpose and requirement of the inspection, an onsite inspection will need to be performed when travel restrictions are lifted.

1.6. Would WHO PQT/INS consider a delay in implementation of corrective and preventive actions (CAPA) resulting from an inspection that took place before or during the Covid-19 pandemic?

It is expected that CAPA corresponding to WHO PQ inspections conducted before or during the COVID-19 outbreak are submitted within the set deadlines. However, if justifiable, the organization may contact the respective inspection team and request for an extension of the deadline for CAPA submission.

1.7. Would WHO PQT/INS encourage a more structured meeting to discuss pending inspection issues with organizations, via suitable online communication tools?

Yes, WHO PQT/INS would welcome suitable online communication tools meetings to discuss pending inspection issues provided the concerned organization provides in advance an agenda with the topics for discussion and considering availability of inspection team members.

1.8. What measures will be taken by WHO PQT/INS in respect of WHO Public Inspection Reports (WHOPIRs) for establishments where the validity of the reports had lapsed, and no inspection has been conducted due to restrictions linked to the COVID-19 pandemic?

As a consequence of the pandemic and in view of the various international and national travel restrictions preventing the conduct of an on-site GxP inspection, the published WHOPIR will remain valid as per the scope and site activities of the published WHOPIR and until the report has been replaced by a WHOPIR with a later date. On-site inspections will be resumed once travel restrictions are lifted and inspections will be conducted following the WHO PQT/INS risk-based inspection planning procedure.

Should any clarification pertaining to the published WHOPIRs be required, please contact WHO PQT/INS at prequalinspection@who.int.

2. QUESTIONS RELATED TO QUALITY MANAGEMENT SYSTEMS (QMS)

2.1. What are the regulatory expectations in terms of applying QMS principles during the COVID-19 pandemic?

It is acknowledged that the COVID-19 pandemic has a significant impact on people and businesses around the world and in many cases, re-prioritization of business activities is necessary in order to continue operations. Business continuity and disaster plans should be deployed, where applicable. The definitive aim should be to ensure the quality, safety, efficacy and continuity in the supply of products and services to meet a high level of public health and protect human lives.

Top/senior management has the responsibility of ensuring an effective QMS is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organization.

It is expected that organizations located in countries where the COVID-19 pandemic does not have a significant impact and create constraints on everyday operations, operate under the implemented QMS, as usual. For organizations located in countries where the COVID-19 pandemic has led to significant disruptions in everyday life and operations, it is expected that top/senior management with the assistance of expert personnel review their QMS, using risk management principles in order to identify hazards, estimate the risk associated with the identified hazards, compare the identified and analysed risks against established criteria, decide to reduce and/or accept risks, share information about the risks and risk management plan with concerned personnel and finally review and monitor the output of the risk management process. It is expected that all key operations and processes are included in the risk management process to protect human lives and public health. Detailed records of the application of risk management principles should be maintained.

Following the implementation of risk management principles, it may be necessary to adjust some processes and operations in order to continue operating under the QMS, establish new procedures and/or revise existing ones. These changes should be appropriately justified, assessed and documented using the existing change management system. If departures from the QMS principles and established procedures and processes are unavoidable during the COVID-19 pandemic, then the organization has to justify and evaluate these deviations and follow the deviation/non-conformance procedure.

A plan for transition back to the normal state should also be established based on local/national/international recommendations considering risk management principles in order to facilitate return to the routine operations and activities after the pandemic state is lifted.

3. QUESTIONS RELATED TO PERSONNEL

3.1. What should personnel do to ensure compliance with QMS principles and regulatory standards during the COVID-19 pandemic?

Top/senior management is responsible for identifying key operations to be maintained during the pandemic and personnel to work on/off-site based on risk management principles taking into account national regulations, guidance and measures.

Selection of key operations and personnel should be justified and documented. Operations that could be performed remotely without compromising the QMS principles, should be encouraged. Consideration should be given to prevent the spread of the virus within the organization by limiting the number of personnel in the premises, where appropriate and by applying suitable organizational measures which should be justified, documented and monitored. More specifically, measures to be considered include but not limited to:

a. Developing a contingency plan in case any employee or subject (relevant to CROs only) is tested positive for COVID-19.
b. Providing remote training on extra hygiene measures and procedures.
c. Encouraging personnel to stay home if sick, or if any member of their family is sick and to report to the organization's physician or authorities for prompt identification and isolation.
d. Encouraging personnel to avoid public gatherings and using crowded public transport.
e. Implementing body temperature control before entry to the facilities.
f. Implementing frequent hand washing with soap and water and the use of hand disinfectant, where appropriate.
g. Reminding personnel to avoid touching their eyes, nose, and mouth with unwashed hands.
h. Increasing physical distance between employees or limiting the number of employees in a specific room/area (e.g. personnel change rooms, canteen, clean areas).
i. Avoiding face-to-face work area designs.
j. Using disposable personal protective equipment (e.g. masks, gloves, goggles, shoe coverings, coveralls, gowns) or reducing the duration of use of re-usable personal protective equipment.
k. Avoiding visitors or contractors entering the facilities during the pandemic, unless necessary and ensuring that extra hygiene measures are applied and visitors are observed from a safe distance during their visit.

4. QUESTIONS RELATED TO FACILITIES AND EQUIPMENT

4.1. How should facilities and equipment be maintained at suitable operational states during the COVID-19 pandemic?

In general, manufacturing facilities and equipment are expected to be cleaned and sanitized, where appropriate, according to established procedures. The organizations should review and evaluate the cleaning/disinfection agents and intervals and ensure that the cleaning frequency and methods provide sufficient protection when contamination is suspected or confirmed due to coronavirus. Where new cleaning agents or disinfectants are to be applied, consideration should be given to not adversely affect the product or service and the operations performed in the room/with the equipment.

In clean areas where Heating Ventilation and Air-conditioning (HVAC) systems are used, additional engineering controls (e.g. increased ventilation rates, use of physical barriers) should be evaluated and considered if there is a risk of coronavirus contamination. Similarly, close monitoring of cleanroom process controls such as air filtration, positive air pressure and air flow patterns to ensure proper function, should be assessed and implemented based on risk management principles.

Where facilities, systems, utilities and equipment need to be qualified, calibrated, verified and maintained, it is expected that the existing procedures are followed (see also Q&A 3.1). However, during the pandemic, it may not be possible for contractors to provide engineering, maintenance, qualification and calibration support. Risk assessments should be conducted on the suitability of facilities, systems, utilities and equipment beyond their calibration/maintenance due date and if used beyond their calibration/maintenance due date, the deviation/non-conformance procedure should be followed. If it is deemed necessary to maintain, qualify or calibrate equipment the following alternatives should be evaluated and applied and any additional measures as necessary with appropriate documented justification:

a. Send equipment off site for requalification, calibration or maintenance to service providers, where possible. Upon receipt of the equipment back on site, verify its status, maintain necessary records and appropriately clean/disinfect before use. Consideration should be given to performing installation qualification, where necessary.
b. Calibration or maintenance of equipment, facilities, utilities, systems to be remotely performed by the contractor using electronic means under the supervision of the organization.
c. Calibration or maintenance to be performed by an appropriately trained employee under the remote supervision of the contractor (e.g. video-conference).
d. Where equipment/system has two or more calibrated instruments measuring the same parameter and located in close proximity (e.g. thermometer for visual control and recording thermocouple of a cold room), the instrument with valid calibration status may be used to verify the validity of readings of the second instrument that is beyond its calibration due date, provided a documented risk assessment is performed and the outcome indicates that the risk is acceptable.

5. QUESTIONS RELATED TO MATERIAL

5.1. How should organizations handle incoming materials and release of finished products?

Materials received from external sources should be handled carefully to avoid any risk of contamination. In particular,

a. Consideration should be given to clean and sanitize incoming materials received in their original containers or packs using suitable methods and sanitizers before transferring them to the warehouse storage.
b. Cleaning, sanitization and disinfection procedures should not compromise the quality of the materials nor the safety of the personnel.
c. Sampling of incoming material should be performed following the approved procedure(s). The organizations should not reduce the established sampling process for APIs received for manufacturing finished products unless reduced sampling is appropriately validated in accordance with relevant guidelines.
d. Finished products should only be dispatched when they are fully tested and released. Poor hygiene practices should not lead to potential contamination or cross-contamination of the dispatched products with the coronavirus.
e. Appropriate measures should be in place to track and trace the involvement of personnel, use of equipment and utilities. Adequate controls should be in place to ensure the product is stored under hygienic and approved conditions before it is shipped, during transit and considering possible delays in transit warehouses.

6. QUESTIONS RELATED TO PRODUCTION

6.1. How should organizations continue to run production activities during the COVID-19 pandemic?

Top/senior management is responsible for identifying key operations to be maintained during the pandemic and personnel to work on/off-site based on risk management principles taking into account national regulations, guidance and measures (see also Q&A 3.1).

In case contract workers are used, the organizations must ensure that the same hygiene and health requirements as for permanent employees are followed. Production and packaging operations should be performed according to established procedures. It should be ensured that any extra hygiene measures don't adversely affect the quality of products and are documented.

Documented evidence should be made available with each production and packaging activity performed to ensure traceability of personnel and operations. Process validation activities including media fills simulations should be performed in accordance with established procedures.

7. QUESTIONS RELATED TO QUALITY CONTROL LABORATORIES (MANUFACTURERS, NATIONAL AND PRIVATE LABS)

7.1. How do QCLs ensure activities are appropriately running during the COVID-19 pandemic?

Testing starting and packaging materials, intermediates and finished products are one of the main tasks of the quality control units and by independent (national and private) quality control laboratories. It must be ensured that all appropriate tests are conducted on incoming goods, materials and finished products and released only after their quality has been judged as satisfactory, as per usual practice. If national or private QCLs are responsible to perform testing as part of the batch release, the authorized person should continue to ensure completeness of testing before a product is released for sale. Contingency plans should be in place should the authorized person become infected or unable to perform his/her duties.

The laboratory equipment and instruments should be qualified/ calibrated (see also Q&A 4.1) and handled appropriately such that they do not become a source of infection or cross-contamination of the coronavirus.

Additional cleaning and sanitization should be carried out for all surfaces, including surfaces that personnel are likely to touch, such as keyboards, mouse and computer screens associated with HPLC, GC, FTIR, UV-VIS and other laboratory equipment.

7.2. Are QCLs allowed to perform skip or reduced testing during the COVID-19 pandemic?

It is the responsibility of the organizations to perform complete testing of incoming materials, intermediates and finished products following agreed specifications and method of analysis.

A science and risk-based approach for the evaluation and implementation of a reduced or skip testing program for the release of starting materials, intermediates, APIs, excipients, packaging components and finished products may be considered in accordance with regulatory guidelines. Organizations are required to notify their competent regulatory authorities and WHO PQT of their intention to conduct skip or reduced testing before its implementation. Based on the submitted evidence supporting documentation, a decision on the acceptance/rejection for skip testing will be communicated accordingly.

7.3. Are QCLs allowed to perform skip or reduced testing on stability study samples during the COVID-19 pandemic?

Skip or reduced testing may be considered for on-going stability studies. Organizations are required to notify their competent regulatory authorities and WHO PQT Unit of their intention to conduct skip or reduced testing before its implementation. Based on the submitted evidence supporting documentation, a decision on the acceptance/rejection for skip testing will be communicated accordingly.

REFERENCES

https://www.who.int/medicines/areas/quality_safety/quality_assurance/en/

WHO TRS 1010 Annex 9, Guidance on Good Practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions

WHO TRS 986 Annex 2, WHO Good Manufacturing Practices for pharmaceutical products: main principles

WHO TRS 957 Annex 1, WHO Good Practices for pharmaceutical quality control laboratories

WHO TRS 961 Annex 2, WHO Good Practices for pharmaceutical microbiology laboratories

WHO TRS 981 Annex 2, WHO Guidelines on quality risk management

WHO TRS 937 Annex 4, Supplementary Guidelines on Good Manufacturing practices: validation

Quality management systems – Requirements, International Standard (ICS 03.120.10), 5th edition (2015), ISO/FDIS 9001: 2015 Short name: ISO 9001:2015
https://www.iso.org

Medical devices — Quality management systems — Requirements for regulatory purposes ISO 13485:2016

USEFUL LINKS RELATED TO COVID-19

https://www.who.int/news-room/detail/20-04-2020-joint-statement-by-wto-director-general-roberto-azev%C3%AAdo-and-who-director-general-tedros-adhanom-ghebreyesus

EC guideline related to COVID -19: https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf

EMA publication of Q&A related to COVID-19: https://www.ema.europa.eu/en/news/update-guidance-regulatory-expectations-context-covid-19-pandemic

FDA Guideline: http://www.fda.gov/cder/guidance/index.htm

MHRA Blog relating to measures implemented on COVID-19:
https://www.gov.uk/guidance/exceptional-good-distribution-practice-gdp-flexibilities-for-medicines-during-the-coronavirus-covid-19-outbreak

TGA, Australia publication on notification of suspending international inspection programme
https://www.tga.gov.au/media-release/tga-suspends-overseas-gmp-inspections-and-qms-audits-until-further-notice