Dear Dr Sriram,

Subject: WHO Prequalification of Diagnostics – Notice of Concern

Sites of manufacture: Tulip Group (Qualpro Diagnostics, Orchid Biomedical Systems, Zephyr Biomedicals).


Products: PQDx numbers: Product codes:
Retrocheck HIV PQDx 0011-009-00 40501001, 40501010, 40501025, 40501050, 40501100
(Qualpro Diagnostics) 
Paracheck P.f. Device PQDx 0070-024-00 30301005, 30301010, 30301025, 30301100
(Orchid Biomedical Systems)
Paracheck P.f. Dipstick PQDx 0071-024-00 30302010, 30302025, 30302100
(Orchid Biomedical Systems)
Parascreen Pan/P.f. PQDx 0074-025-00 50310001, 50310010, 50310025
(Zephyr Biomedicals)

The first inspection of the sites of manufacturing of the above mentioned products was conducted by the WHO Prequalification of Diagnostics Programme from 25-29 October 2010 at the Verna Industrial Estate, Goa, India. Due to the number and significance of the nonconformities identified, a re-inspection of the facility was planned. A re-inspection took place 28–30 November 2011.

Important note: As the Tulip Group is established under a single quality management system and as an inspection of this type is a sampling exercise, the examples below cover the two manufacturing sites and three listed companies, Qualpro Diagnostics, Orchid Biomedical Systems and Zephyr Biomedicals. The detailed examples of these and other nonconformities are recorded in the WHO re-inspection report.

At the re-inspection, the inspection team found that the manufacturer had not effectively implemented corrective actions according to their own action plan from the first inspection. The re-inspection revealed a significant number of additional critical nonconformities, and that a
number of critical and major nonconformities identified in the first inspection had not been fully addressed. The manufacturer provided an action plan to WHO on 23 April 2012 that contained the planning to address the nonconformities listed in the WHO re-inspection report. However, this response did not satisfactorily address all of the critical and major nonconformities.

It should be noted that in accordance with international best practice, nonconformities that remained unaddressed are escalated to a more serious level. Reference is made to GHTF/SG4/N28R4:2008 ‘Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 1: General Requirements’ and GHTF/SG3(PD)/N19 - Proposed Document: ‘Quality management system – Medical devices – Nonconformity Grading System for Regulatory Purposes and Information Exchange’. That is, if a nonconformity that was identified in the first inspection was declared a Major Nonconformity and was found to still exist in the re-inspection, the nonconformity was raised to a Critical Nonconformity status.

The following examples are a brief summary of the issues that were not satisfactorily addressed in the manufacturer’s corrective action plan. They are taken from the re-inspection report and include critical nonconformities. Generally even a single critical nonconformity is indicative of a serious breach in the effectiveness of the quality management system. Reference is made to ISO 13485:2003 – Medical devices – Quality management systems – Requirements for regulatory purposes.

The following nonconformities were raised at this re-inspection. These nonconformities were identified at the re-inspection as of major concern and will remain open until confirmation of rectification is achieved at a second re-inspection.

**Critical nonconformity (NC) 1: lack of raw data to support performance claims.**
Reliable and clear data and documentation must be submitted, and be readily available, for review by the WHO inspection team. Lack of raw data was widespread, raising serious doubts about many processes. Lack of implementation of deviation reporting also remained a critical nonconformity.

*Requirement:* ‘Records shall be established and maintained to provide evidence of conformity to requirements and of the effective operation of the quality management system. Records shall remain legible, readily identifiable and retrievable’. (Refer ISO 13485:2003 4.2.4 Control of records).

The following examples raised concern:

1. Potentially misleading raw data for in-process testing of Retrocheck HIV whereby non-reactive test results were recorded but no negative sera were seen by the inspection team to be tested.
2. When reading two cassettes for in-process QC checks on Retrocheck HIV, test readings were reported as one plus (1+), when the results were clearly negative as observed by the inspection team.
3. Potentially misleading information related to batches submitted for the WHO laboratory evaluation component of prequalification for Retrocheck HIV. At the inspection, it was revealed that the two batches were not significantly different from each other.

**Critical nonconformity 2: inadequate control of production and batch release.**
Inadequate evidence of QC staff training and empowerment, poor traceability, poor record keeping including inadequate raw data records and inadequate control samples used to ensure lot release met sensitivity criteria.

*Requirement:* ‘The organization shall plan and carry out production and service provision under controlled conditions’. (Refer ISO 13485:2003 7.5.1 Control of production and service provision).
Major nonconformity 1: lack of independence and authority in key positions.
Requirement: ‘Top management shall establish the interrelation of all personnel who manage, perform and verify work affecting quality, and shall ensure the independence and authority necessary to perform these tasks’. (Refer ISO 13485:2003 5.5.1 Responsibility and authority).

Major nonconformity 2: regulatory requirements not met.
Retrocheck HIV was presented to the WHO Prequalification of Diagnostics programme as meeting the requirements of the European Directive 98/79/EC on in vitro diagnostic medical devices (IVDD). Such compliance allows for a ‘fast track’ prequalification approach. The following issues were noted:

a) The product design file (dossier) examined (Retrocheck HIV), that was reportedly submitted for EC conformity assessment, did not give any information about the actual design of the product i.e. no raw data, no information about all of the materials and components tested (and the components rejected); no characterization or studies of the antigens sequence (or those rejected); and no characterization of the migration membrane or the conjugate pad (and also the ones rejected). It did not give any information about the ratio of coupling expected for each conjugate, the purity of the conjugate obtained, the reproducibility and repeatability of the selected protocol for coupling, and no information about the calibration of the conjugates.

b) The performance evaluation of the product did not systematically mention the batch number of the products sent for evaluation; no external studies demonstrated both specificity and sensitivity on the same batches in the same evaluation. (Refer ISO 13485:2003 7.2.1 c Customer related process – statutory and regulatory requirements related to the product).

In addition, previous nonconformities were not adequately addressed. At the re-inspection, evidence of compliance with the action plan submitted by the manufacturer in response to the first WHO inspection report was sought. Although some issues had been satisfactorily addressed, many systemic issues remained unaddressed, thus the nonconformities could not be closed out and therefore remain open.

Previous critical nonconformities:
1) Previous critical nonconformity “Failure to demonstrate validity of critical parameter (stability) studies with records of raw data” remained open.
   Requirement: Records shall be established and maintained to provide evidence of conformity to requirements and of the effective operation of the quality management system. Records shall remain legible, readily identifiable and retrievable. (Refer ISO 13485:2003 4.2.4 Control of records).

2) Previous critical nonconformity “Staff training (notably in the area of deviation reporting and investigation) was insufficient” remained open. Previous critical nonconformities “Lack of appropriate response to nonconforming product; deviations were not raised when needed” and “Failure to adequately demonstrate conformity of product” also remained open.
   Requirement: The organization shall ensure that product which does not conform to product requirements is identified and controlled to prevent its unintended use or delivery. The controls and related responsibilities and authorities for dealing with nonconforming product shall be defined in a documented procedure. (Refer ISO 13485:2003 8.3 Control of nonconforming product).
3) Previous critical nonconformity “Infrastructure maintenance and work environment were insufficient” remained open.
   Requirement: The organization shall determine, provide and maintain the infrastructure needed to achieve conformity to product requirements. (Refer ISO 13485:2003 6.3 Infrastructure).

4) Previous critical nonconformity “Lack of assurance that production was well controlled” remained open. (Refer ISO 13485:2003 7.5.1 Control of production and service provision).
   The following issues were noted: no SOP for pad cutting operation; label defects were not recorded; no reject bins available; batch record had no manufacturing date assigned and was kept in closed drawer (not filled out as process continued); in-process sampling was unclear – no systematic sampling for QC could be seen during production and assembly; no calibration of conjugate was done (only optical density); no calibration record was available for Biodot striping machine; silica gel and membrane were stored in areas without humidity control.

These issues are fundamental quality management system requirements and rectification would have been expected following the first WHO inspection.

5) Previous critical nonconformity “Lack of assurance that validation processes were adequate” remained open. (Refer ISO 13485:2003 7.3.6 Design and development validation).

6) Previous critical nonconformity “Lack of assurance that identification and traceability were adequate” remained open.
   Requirement: ‘The organization shall identify the product by suitable means throughout product realization, and shall establish documented procedures for such product identification.’ (Refer ISO13485:2003 7.5.3 Identification and traceability).

**Previous major nonconformities:**

1) Progress had been made but previous major nonconformity “Lack of assurance that product conforms to specified purchase requirements” remained open.
   Requirement: ‘The organization shall monitor and measure the characteristics of the product to verify that product requirements have been met (Refer ISO 13485:2003 8.2.4 Monitoring and measurement of product).

2) Previous major nonconformities “Equipment maintenance was generally poor and poorly documented” and “Lack of control over monitoring and measuring devices” remained open. (Refer ISO13485:2003 6.3 Infrastructure & 7.6 Control of monitoring and measuring devices).

3) Previous major nonconformity “Failure to adequately ensure conformity and to maintain the effectiveness of the quality management system; lack of adequate monitoring and measurement of key quality indicators and subsequent improvement activities; insufficient evidence of management review able to meet quality objectives” remained open.
   Requirement: Top management shall ensure that quality objectives, including those needed to meet requirements for product [see 7.1 a], are established at relevant functions and levels within the organization. The quality objectives shall be measurable and consistent with the quality policy. (Refer ISO 13485:2003 5.4.1 Quality objectives).
4) Previous major nonconformity: “Lack of adequate documentation and document control” remained open.

Requirement: ‘The quality management system documentation shall include ...d) documents needed by the organization to ensure the effective planning, operation and control of its processes.’ (Refer ISO 13485:2003 4.2.1 d).

Summary

In summary, although some improvements had been made since the first inspection and some of the planned corrective actions submitted in the action plan appeared to be appropriate, the re-inspection and the subsequent action plan showed that the overall effectiveness of the quality management system at the Tulip Group, Inc. remained inadequate. This requires considerable rectification and confirmation before confidence in the quality of the products being produced by the Tulip Group is re-established.

Based on these findings, WHO will withhold prequalification of all active applications for products manufactured at the above mentioned sites, and close any other applications received. This will remain in effect until these nonconformities have been satisfactorily addressed and WHO has verified and confirmed the acceptability of the corrective actions.

Should you wish to comment on this Notice of Concern, you are advised to email the undersigned, with details, to diagnostics@who.int. The matter will be investigated and unless advised otherwise, you can expect to receive a response within 15 working days. All feedback will be treated in confidence and without prejudice. However, this correspondence will not influence the immediate publication of the Notice of Concern.

Publication of this Notice of Concern

In accordance with WHO procedures, WHO will publish this Notice of Concern on the WHO website. Please note that a Notice of Concern will remain active on the WHO website until WHO has confirmed the requirements for WHO Prequalification of Diagnostics have been fulfilled.

Yours sincerely,

(Signature)

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