Quality Assurance (QA) for Health Products

QA Information Notice

IN Nº 2019-03 **Version: 13/05/2019**	**TGF Position on the UK MHRA Statement of non-compliance with Good Manufacturing Practices (GMP) for Micro Labs Limited, Unit 3, Hosur (India)**

Addressees

- Any person having products in stock, in transit or under custom clearance through PRs / For Information Only
- National Regulatory Authorities and/or Pharmacovigilance Centers through PRs/ For Information Only

Purpose

The Global Fund Quality Assurance Team is issuing this Information Notice to forward information regarding **a statement of non-compliance with Good Manufacturing Practices (GMP)** published on the 24th of January 2019, by the UK National Medicines Regulatory Authority namely UK MHRA for the manufacturing site **Unit 3** of Micro Labs Limited, located at 92 SIPCOT Industrial Complex in Hosur (India).

Identification of the product(s) and manufacturer

Name of Manufacturer/Manufacturing Site	Micro Labs Ltd, Unit 03, 92 Sipcot Industrial Complex, Hosur, Tamil Nadu, 635 126, India.
INN Name	(Products used for treatment of tuberculosis (TB) as listed in Annex A)
Commercial Name(s)	
Pharmaceutical form	
Strength	
Packaging & Pack size	
Batch(es)	
Expiry Date	

Background

The inspection of the UK MHRA performed in November 2018 identified failures in the cross-contamination controls applied by the manufacturer resulting in a risk of cross contamination.

Based on the above, the UK MHRA withdrew the current GMP certificate, issued a statement of non-compliance and recommended prohibition of supply except for products critical to patient safety. The UK MHRA also recommended to consider the recall of any products based on a quality risk assessment. The statement of non-compliance has been published and made publicly available via the Eudra GMP database.

Nature of defect(s)

Details of defect or problem.	**Failure in the cross-contamination controls applied by the manufacturer**
Is there any evidence or suspicion of a risk to public health?	**Investigations are on-going**
Extent of the problem (eg. how many batches).	**Multiple batches of various pharmaceuticals products** **While waiting for outcomes of the investigations, the present notice is extended to all medicines manufactured at Hosur Unit 3 site.**
Extent of distribution of the product / batch (es). (based on PQR data)	**Angola, Bangladesh, Bolivia (Plurinational State), Bulgaria, Djibouti, Egypt, Guatemala, Guinea-Bissau, Haiti, Kazakhstan, Korea (Democratic Peoples Republic), Kyrgyzstan, Madagascar, Moldova, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Sao Tome and Principe, Senegal, Somalia, Tajikistan, Tanzania (United Republic), Western Asia, Zimbabwe**
Number of patients potentially impacted	**NA**

Action/Investigations taken

- The UK MHRA decision of withdrawing the GMP certificate makes reference to the European medicine Agency (EMA) guideline related to the "setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"[2] applied for cleaning validation purposes based on the method for establishing the so-called Permitted Daily Exposure (PDE).

- Cleaning is a risk reducing measure and carry-over limits for cleaning validation studies are widely used in the pharmaceutical industry. QA Team recognized that a variety of approaches are taken to establish these limits and not all regulatory systems have yet integrated the concept of PDE in their own guidance document. Such difference may lead to some divergence in the findings when verifying GMP compliance with the cleaning validation requirements.

- GF liaise with GDF on current procurement risks and in particular to identify products critical to patient safety

- We have been informed by the Manufacturer that the Qualified Persons (QP) of the manufacturer's license holder, performed an audit during the week of the 25th of February 2019. This audit aimed to monitor and assess progress against the rectification of the deficiencies noted by the UK MHRA. The QP confirmed that in their opinion the facility to be operating in compliance with the requirements of the EU GMP, with satisfactory progress towards resolution of the UK MHRA "Major" Inspectional Observations.

- WHO PQ published on the 8th March 2019 a response to the UK MHRA Statement of Non-compliance[1]. In this response, WHO recalls that they conducted an inspection in July 2017 and that the prequalification status remains current. WHO obtained information including risk mitigation strategy from the manufacturer and doesn't consider that a recall of WHO prequalified products is necessary.

- We have also been informed by Micro Labs Ltd, that the German medicine regulatory authority "Bundesinstitut für Arzneimittel und Medizinprodukte" authorized on the 19th of March 2019 Albendazole 400 mg chewable tablets that is manufactured at Micro Labs Ltd, Unit 03, 92 Sipcot Industrial Complex, Hosur, Tamil Nadu, 635 126, India.

- During the week of the 8th of April 2019, a joint follow-up inspection involving the UK MHRA, WHO PQ and UNICEF was conducted. According to a statement from WHO PQ, the inspectors reported that the site had implemented the proposed CAPA as per the MHRA requirements.

Decisions / Next Steps

Based on the information available to date providing increased assurance that the corrective actions have been adequately implemented, TGF QA team advise to maintain the eligibility for procurement of the products manufactured at Hosur Unit 3 site and procured for Global Fund grants until further notice.

Understanding the increased assurance provided by such improvement in the requirements for cleaning validation, TGF QA Team will engage with WHO PQ to consider increased harmonization on this topic.

GF Contacts and acknowledgement

This Information Notice is for information purposes only and does not require a specific written response from the PR.

Please direct any questions about this matter to the technical contacts listed below.

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Annex A : List of medicines manufactured at the Micro Labs Limited, Hosur Unit 3 Site

Designation of Pharmaceutical products	TGF Quality Standards
• Clarithromycin Tablet 250mg	SRA
• Clarithromycin Tablet 500mg	SRA
• Ethionamide Disp. Tablets, 125 mg	GF-ERP
• Ethionamide Tablet, Film-coated 125 mg	WHO-PQ
• Ethionamide Tablet, Film-Coated 250 mg	WHO-PQ
• Isoniazid Tablet 100 mg	WHO-PQ
• Isoniazid Tablet 300 mg	WHO-PQ
• Levofloxacin Disp. Tablet, 100mg	GF-ERP
• Levofloxacin Tablet, Film-Coated 250 mg	WHO-PQ
• Levofloxacin Tablet, Film-Coated 500 mg	WHO-PQ
• Levofloxacin Tablet, Film-Coated 750 mg	GF-ERP
• Moxifloxacin (hydrochloride) Tablet, Dispersible 100mg	WHO-PQ
• Moxifloxacin (hydrochloride) Tablet, coated 400mg	WHO-PQ
• Protionamide Tablet, Film-Coated 250 mg	WHO-PQ
• Pyrazinamide Tablet 400 mg	WHO-PQ
• Pyrazinamide Tablet 500 mg	WHO-PQ

References:

1. WHO response to UK MHRA Statement of Non-Compliance with GMP on Micro Labs Hosur (Unit 03) manufacturing facility situated at Hosur (Tamil Nadu, India)
2. Setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
3. Annex 3- Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation