WHO response to US FDA regulatory actions regarding Ranbaxy Laboratories Ltd’s Toansa site

Following its finding of severe failures to comply with pharmaceutical good manufacturing practices (GMP) during an unannounced inspection 5‒11 January 2014 (1) of the Toansa Punjab, India, facility, of Ranbaxy Laboratories Limited (hereafter referred to as Ranbaxy), US FDA issued a statement on 23 January 2014 that it had notified Ranbaxy that it is prohibited from distributing active pharmaceutical ingredients (APIs) within the USA, that have been manufactured at its facility in Toansa, India, for use in production of FDA-regulated drug products.i

Are WHO prequalified products impacted by these findings?

WHO has prequalified four finished pharmaceutical products (FPPs) manufactured by Ranbaxy which are authorized to be formulated with APIs manufactured at Ranbaxy’s Toansa facility, as well as with other WHO-approved APIs, produced by other manufacturers. Current prequalified Ranbaxy FPPs are listed on the website of the WHO Prequalification of Medicines Programme at www.who.int/prequal. These products are:

1. HA356: Lamivudine/zidovudine + efavirenz (2 + 1) x 15 tablets, 150/300 mg + 600 mg
2. HA357: Lamivudine/stavudine + efavirenz aluminium/aluminium co-blister, (2+1) x 15, 150/30 mg + 600 mg
3. HA358: Lamivudine/stavudine + efavirenz - (2 + 1) x 15, 150 mg/40 mg + 600 mg
4. HA423: Tenofovir disoproxil (fumarate) tablet, film-coated 300 mg.

Some of the APIs authorized for use in production of the above Ranbaxy products are manufactured at Ranbaxy Toansa. Alternative sources of these APIs, from other API manufacturers other than Ranbaxy, are also approved by WHO.

What action is being taken by WHO?

The extent to which the poor practices uncovered during US FDA inspection apply to the testing and manufacturing processes for WHO-prequalified products are, as yet, unclear. WHO inspectors inspected the Toansa site in June 2013 and major deficiencies were noted, including in relation to the company’s laboratory management control systems. WHO is currently reviewing Ranbaxy’s recent communication regarding its implementation of corrective and preventive action in response to the deficiencies noted.

As a precautionary measure and with immediate effect:

- WHO authorization of use of APIs manufactured at the Ranbaxy Toansa facility, for production of WHO-prequalified products, is suspended
- all WHO assessment of APIs manufactured at the Ranbaxy Toansa facility, for which an application for WHO prequalification has been made, is suspended.
Together with its international regulatory Partners, WHO will review information contained in related US FDA reports and action the agency has taken. It will also gather and analyse further information, including the outcomes of other recent GMP inspections performed at the company’s manufacturing sites by inspectorates of European Union member states and other members of the Pharmaceutical Inspection Convention and Pharmaceutical Co-operation Scheme (PIC/s). ii

Advice to national medicines regulatory authorities (NMRAs)

The Toansa Ranbaxy facility manufacturers over 100 APIs, many of which are used in the manufacture of essential medicines. APIs manufactured at the Toansa facility are used to produce numerous Ranbaxy products and many of those of other pharmaceutical manufacturers; they are available on markets worldwide.

At this time WHO has no direct evidence that Toansa APIs, and the formulations that contain them, represent a critical health risk, sufficient to recommend recall of products. Since supply shortages of medically necessary formulations could arise in the absence of supplies from Ranbaxy Toansa, WHO and a number of NMRAs will ascertain supply and alternative supply options before finalizing their regulatory actions.

Inevitably, actions may differ since different suppliers — for both the APIs and the manufacturers of relevant finished formulations — will be registered in different countries. Supply of specific APIs from Toansa and products manufactured with these APIs may therefore be suspended in some territories, but not in others.

Advice to procurers

Poor GMP practices — particularly those that lead to provision of misleading information by a pharmaceutical manufacturing company — are to be condemned. Clearly, the history and practices of a company, and specifically its site of API manufacture or API source, should be considered when any medicines procurement is undertaken.

Advice to patients taking Ranbaxy products

Despite the serious problems uncovered at the Ranbaxy Toansa site by the US FDA inspection, there is at present no available evidence to suggest that finished Ranbaxy products currently prequalified by WHO represent a risk to patients taking these medicines. WHO has verified that, since 2010, none of Ranbaxy’s prequalified products has contained or used API produced at the Toansa site. Moreover, authorization to use any APIs manufactured at the Toansa site, in the production of WHO-prequalified Ranbaxy products, is now suspended. Patients should therefore continue to take their prescribed course of treatment and take medical advice before terminating treatment.

Further information

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1 US FDA press release on Ranbaxy Toansa: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm382736.htm

2 The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which facilitate active and constructive co-operation in the field of GMP. See: http://www.picscheme.org