

Regulators slate Roche 'lack of knowledge and understanding' in Viracept contamination case

By Anna Lewcock

23/11/2007- The official report into good manufacturing practice (GMP) failures that caused dangerous contamination and a Europe-wide recall of Roche's HIV drug Viracept (nelfinavir) claims the firm simply did not understand its own manufacturing processes.

The Committee for Medicinal Products for Human Use (CHMP) published its assessment yesterday, recounting the inspections and discussions that took place in the wake of the June recall and noting the "*critical GMP deficiencies*" that resulted in the suspension of Roche's Viracept marketing authorisation.

The European Medicines Agency (EMA) carried out an inspection of Roche's active ingredient manufacturing facility in Basel in collaboration with Swiss regulators Swissmedic, to assess conditions at the plant where the contamination occurred.

Their examination revealed violations that not only led to the high-level contamination reported over the summer, but also led to questions regarding regular manufacturing processes and concerns over "*the quality of Viracept and its safety under normal conditions of use.*"

Inspection findings

The regulators' June inspection was prompted by high levels of the genotoxic compound ethyl mesylate (EMS) in the final Viracept drug product, revealed when patients reported their tablets had a strange smell.

Initial reports quickly identified a holding tank used in the drug manufacturing process as the key culprit responsible for the EMS contamination, but further details of Roche's GMP failings weren't available until the CHMP assessment was released yesterday.

It appears that the holding tank, used to store methanesulfonic acid (MSA,) the starting material for the last step of the drug's manufacturing process, was not part of Roche's cleaning Standard Operating Procedure (SOP).

The tank, in fact, was not cleaned *at all* between 2001 and the end of the company's April 2006 production run.

Following non-routine maintenance, the holding tank was then cleaned using ethanol according to SOP guidelines. Crucially, however, the tank was not dried afterwards to rid it of any residual ethanol.

The tank therefore still contained the alcohol when it was charged with the starting material, MSA. This resulted in a reaction that caused high levels of EMS in the Viracept starting material.

This tainted mixture was then used for the October 2006 production campaign and, according to retrospective analysis, led to active ingredient with levels of EMS from 1ppm to 8ppm - significantly higher than the 0.6ppm that represents the Threshold for Toxicological Concern (TTC).

However, leftover MSA that had not been used for the October 2006 run then sat in the holding tank for three months, until the start of the next production run in January 2007. This lengthy storage time allowed the formation of even higher levels of EMS, contaminating the resulting batches with up to 2,300ppm of the harmful compound.

Further exacerbating the problem is the fact that another impurity present in MSA, methyl methanesulfonate (MMS), can be transformed into EMS through the spray-drying process used in the production of Viracept.

Given the apparent lack of attention paid to these aspects of the manufacturing process prior to the EMS spike over the summer, batches manufactured prior to the October 2006 and January 2007 production runs were also tested for EMS.

Results showed EMS levels of 4-10ppm in June 2004 batches and 100-120ppm in June 2005 runs - again, much higher than current guidance for genotoxic impurities recommends.

Roche didn't understand

Perhaps one of the most unnerving aspects of the CHMP's findings was its opinion that one of the root causes of contamination during Viracept's history was the *"lack of knowledge and understanding with regard to the manufacturing process"* exhibited by the drug's manufacturer.

"This may be due to the fact that the production process was originally purchased from another company," the assessment report suggests.

"As the pharmaceutical development was not performed by [Roche], the potential risk for the formation of EMS in the manufacturing process may have been misjudged."

While Viracept itself was indeed developed by Agouron Pharmaceuticals in collaboration with the pharmaceutical arm of Japan Tobacco, Roche has been responsible for the drug for the best part of a decade.

The CHMP inspectors reported one critical and four major deficiencies at the Basel site, and *"discussed numerous preventative measures"* relating to validation of the last step of

the manufacturing process, cleaning procedures and validation, handling of key starting material, analytical testing and training.

The CHMP also criticised the company's initial draft risk management plan and its evaluation of the possible harm associated with EMS:

[The plan] was considered to down play the seriousness of risk, implied low frequency and the section on preventability focussed on recall and communication but did not consider any corrective measures to address the identified issues surrounding the manufacturing processes or the need for long term monitoring of exposed patients."

Roche has now, however, convinced the CHMP and EU regulators that it has amended its Viracept manufacturing procedure satisfactorily (largely by removing the holding tank from the production process) and last month had its Viracept marketing authorisation reinstated.

New limits have been set restricting levels of EMS in the drug's active substance to less than 0.5ppm, but given that data on the compound and its effect on humans is somewhat lacking, Roche is also in the process of carrying out several studies to try and establish just how harmful EMS - and the tainted Viracept - could really be.

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