Bristol-Myers Squibb

Bristol-Myers Squibb Final Quality Risk Assessment – Updated April 11th, 2012

Viaspan

Executive Summary

Viaspan has been manufactured for BMS by Fresenius Kabi Austria since 2006. BMS were notified by Fresenius Kabi on March 19th, 2012 of a media fill failure for the Viaspan manufacturing line . A "media fill" or aseptic process simulation is performed every 6 to 8 months to reconfirm aseptic processing operations for sterile API and drug product.Following a technical review of information provided by Fresenius Kabi, BMS notified the relevant Health authorities regarding the media fill failure starting on March 21th. Then, BMS communicated the decision to recall batches on March 30th, as, despite no evidence of contamination of the Viaspan batches that had been released to the market, BMS could not completely assure that batches manufactured since the last successful media fill were free from contamination.

Since then Fresenius Kabi have completed their investigation and provided to BMS all additional test results performed to evaluate the impact on batches previously distributed to the market as committed in the initial risk assessment. The potential root cause has been confirmed, the impacted scope confirmed as being the batches manufactured between the last successful media fill (July 2011) and the failing media fill (February 2012). However all additional tests performed meet the specifications and do not support evidence for any contamination or potential for contamination of the batches within the scope of investigation. There is therefore a strong demonstration that the batches released to the market since July 2011 are not contaminated however, unless testing individually every single unit of the batches, Fresenius Kabi and BMS will not be able to demonstrate that the batches are all free from contamination. Therefore BMS reiterates that the recall of Viaspan is the best precautionary measure in this case.

Conclusion of Fresenius Kabi investigation:

- A media fill failure occurred at Fresenius Kabi on a dedicated production and filling line
- Bacillus cereus is the contaminant of the media fill. *Bacillus cereus* is an environmental germ that has been previously identified on rare occasion in zone C at Fresenius. The filling takes place in an isolator grade A
- A complete review of components and primary packaging, integrity test of filters, environmental conditions, behaviour of operators did not allow to identify a root cause as no deviation was detected
- During the investigation of the installation itself, a trace of leak was detected outside a valve where a pressure gauge PIC 615 is installed after the last 0.22µm sterilizing filter. Inside the valve a residue of Viaspan was identified on the gasket. In addition, when dismantling the valve and the gauge, Fresenius concluded that the pressure gauge was defective
    - The issue with the gauge remained undetected until this media fill failure
    - PIC 615 was removed from the product line, re-calibrated and re-installed in August 2011

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- The valve was dismantled in grade C area and the gasket tested for microbial contamination. Not surprisingly, mainly contaminants from human origin were recovered.

The most probable root cause for the media fill failure is a defective valve associated with a defective pressure gauge that allows ingress of environmental microorganism likely to be present in grade C area where the valve is located. The problem started likely at the date when the gauge was reinstalled in August 2011.

What are the facts that mitigate the risk for the batches on the market

- The previous media fill performed in July 2011 was satisfactory , therefore the batches manufactured before July 2011 can be considered as out of the scope of the investigation
- Fresenius Kabi manufacture Viaspan by strictly adhering to cGMP to ensure the highest level of Sterility Assurance is guaranteed.
- Sterility Assurance Level of the Viaspan production line is supported by an excellent media fill history since 2006 (zero contaminated units reported for the 12 media fills performed) , a zero rate of sterility test failures (in total for the site, for all products, over 10,000 batches tested) in the past 3 years, excellent environmental monitoring results from the Viaspan Filling Isolator (Grade A and B).
- Regarding the Viaspan batches manufactured from July 2011 to February 2012 and that are potentially impacted,
    - To date no confirmed sterility assurance issue has been observed.
    - All Viaspan batches manufactured from July 2011 to February 2012 passed the initial release sterility test,
    - No deviation was recorded during manufacture
    - All batches were released in compliance to cGMPs.
    - To date no market complaint has been reported to BMS
    - No Adverse Drug Reactions has been reported to BMS for any of the Viaspan batches manufactured from July 2011 to February 2012
- Additional product testing performed by Fresenius Kabi to evaluate the potential "risk" to the Viaspan batches manufactured from July 2011 to February 2012 has been completed,
    - Additional sterility testing performed on 4 Viaspan batches currently on site at Fresenius Kabi Austria has passed sterility test according to EP 2.6.1. The batches were manufactured immediately before and after the media fill failure. Additional bioburden testing being performed on the same 4 Viaspan batches has passed bioburden testing with no microbial recovery recorded. More samples were taken from the end of the filling process in order to better explore if contamination was likely to be present at the end of the filling as observed during the media fill.
    - Additional sterility testing performed on retain samples of all Viaspan batches currently "on hold/ recalled" from the markets has passed sterility test. This result although generated on a limited number of units, confirms that there was no proliferation of contaminant during the storage of the batches.

As such, we conclude based on the information above that at the present time there is no evidence of contamination of the Viaspan batches that had been released to the market.

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- The potential of the product to promote the growth of microorganisms has also been studied:
  - Study of the Growth Behaviour of *B. Cereus* in Viaspan under 4°C and under room temperature storage conditions was performed. Under room temperature storage conditions, the study found *B. cereus* was capable of growth in Viaspan. Under 4°C storage consitions, the study found that *B. cereus* (vegetative and spores cells) was not capable of growth in Viaspan. It is important to note, Viaspan market storage condition is stored between 2°C - 8°C. It was concluded that the composition and storage condition of Viaspan do not promote the growth of the Bacillus species.
  - Finally, Study of *B. cereus* Antibiotic Behaviour (Antibiogram) towards a broad spectrum of antibiotics was performed. *B. cereus* was found to be **sensitive** to the following antibiotics; Clindamycin, Erythromycin, Moxifloxacin, Gentamycin, Imipenem, Linezolid, Tigecyclin and Vancomycin. *B. cereus* was found to be **resistant** to the following antibiotics; Cefepim, Cefuroxim, Pencillin and Ampicillin.

Conclusion:

At the present time, we reiterate that there is no evidence of contamination of the Viaspan batches that had been released to the market. However, unless testing individually every single unit of the batches, Fresenius Kabi and BMS will not be able to demonstrate that the batches are all free from contamination the potential risk of infection to the organ transplant recipient who is immune-compromised, as well as, being debilitated due to organ failure is present.

BMS reiterate that the recall to the end user was the best precautionary measure in this case.

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Reference: Bristol-Myers Squibb interim risk assessment signed on March 29th, 2012

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