

CHIRON|VACCINES

Gaskill Road
Speke
Liverpool
L24 9GR
United Kingdom
Tel: +44 (0) 151 705 5000 Fax: +44 (0) 151 705 5018

To: Dr Cohen

Company: FDA

Fax Number: 00 1 301 827 3381

From: Andy Sneddon

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Subject: MHRA Findings / CV Responses

Dear Dr Cohen,

Please find attached a copy of the MHRA findings together with Chiron Vaccines responses in relation to the UK facility / Fluvirin 2004 campaign.

Regards



Andy Sneddon
Site Director

Response and Documented Impact Assessment to the
2004 Fluvirin Manufacturing Campaign – Inspectorate Findings
by D P Hargreaves and I Rees of the MHRA concluded 30th September 2004

1. **Bioburden**

- 1.1 **Bioburden levels for the 2004 manufacturing campaign were found to be significantly higher by a number of orders of magnitude compared to 2003 and 2002. These levels had been sustained from March 2004 to-date.**
- 1.2 **For example, typical result for 2002 and 2003 were <1cfu/ml with 6 – 8 incidents above ___ cfu.ml, whereas in 2004 the levels have been 10^3 to 10^7 with approximately 50 incidents to-date.**

Response to 1.1 & 1.2

Prior to each batch being approved for further processing, an assessment is performed by QA, which includes a bioburden review.

Assessment of all batches manufactured during the 2004 campaign has been performed and approved by the quality department prior to further processing.

All processing has been conducted in full accordance with the product licence.

The Sterility Investigation report includes consideration of the potential impact of the elevated Bioburden levels in 2004. The data generated substantiates the Quality review process.

- 1.3 **Non-conformance reports were only raised in June for bioburden levels in excess of ___ fu/ml reported over the previous 3 months.**

Response to 1.3

We recognise that deviation reports were not raised until June 2004 for bioburden samples which were greater than the QC alert limit specification. However formal out-of-specification (OOS) reports were raised and communicated by the Quality Control department to Quality Assurance and Manufacturing Operational areas and formally documented.

The first instance of a bioburden result that breached the QC alert limit was on the 05 March 2004 relating to a batch manufactured on the 01 March 2004 (3 day test).

An OOS was raised, documented and communicated as soon as the alert limit was breached. This procedure was followed whenever the QC alert limit was exceeded.

At the time the OOS reports were issued the version of the procedure current at that time (QASP098) required that all potential OOS results required a formal expanded laboratory investigation (including additional testing) before confirmation of laboratory error could be excluded.

QASP098 was updated in June 04 to clarify the position with regard to OOS results obtained for bioburden samples. The updated procedure specifies that Non-conformance reports (NCR) must be raised for all confirmed laboratory OOS results. On issue of this procedure NCR's were raised in accordance with the revised procedure, including retrospectively those relating to all batches manufactured during the 2004 campaign.

- 1.4 An investigation team was instigated in late March / early April to determine the cause(s) of the increased bioburden. Several possible sources have been identified but no conclusions have yet been reached.**

Response to 1.4

A formal investigative team was convened in late March 2004 following the identification, assessment and notification (to the Quality Assurance group) of increased bioburden levels. Prior to the formal team being convened actions were initiated to investigate root cause in early March following notification of the initial OOS.

The formal multi-disciplinary team contained representatives from Production, Quality Assurance, Quality Control and Technical Development. A review of the Fluvirin primary manufacturing process was performed and all potential failure modes relating to the elevated bioburden were identified, with action plans initiated.

Based upon the investigation to date no single factor is the cause of the elevated bioburden, including the scale-up for 2004 campaign. Comparison of the process at the 2003 scale by processing two batches at _____ egg scale did not eliminate the bioburden.

- 1.5 The number of instances of Gram negative organism contamination in a critical (sterile filtration) manufacturing room has increased significantly during 2004.**

Response to 1.5

The environmental monitoring programme in place involves the evaluation by the quality department of all environmental data and applicable trends. As part of the

routine review of environmental data from the formulation suite we identified an increased trend of Gram negative organisms isolated during April and May. To ensure that this trend did not lead to an unacceptable level, we fumigated the whole formulation suite at the end of May. This action was successful, as confirmed by ongoing environmental monitoring.

It should be noted that there are no confirmed isolates of *Serratia spp.*, within the Grade - LAF unit where the aseptic connections were made - a key assessment criteria for further batch processing as part of the Quality Assurance process.

1.6 Organisms found in the bioburden are also found in the environment.

Response to 1.6

We recognise that we are bringing non sterile _____ into the formulation suite for further processing (_____), followed by sterile filtration in a _____ room. The product is transferred into, and within the suite in enclosed vessels in a controlled manner in accordance with written procedures.

Processing is designed to protect the open parts of the process (aseptic connections), whilst the environmental monitoring programme monitors the impact of the process on the environment.

The environmental data indicates that the impact on the facility is minimised, and that no widespread environmental challenge exists.

1.7 Organisms found in the bioburden have also been isolated from the sterile filtered monovalent bulk and from finished product (vials).

Response to 1.7

A full detailed examination and impact assessment was conducted as part of the Fluvirin Sterility Investigation - as documented in section 7.5 of Sterile Filtration and section 9.2 'Summary report on the assembly of sterile connections'.

All the data we have generated clearly demonstrate that the _____ μm filter is effective. Therefore, it can be concluded that the bacterial contamination present in the pre-filtration MBP material would be retained by the _____ μm filter.

The report concludes that the contaminated monoblends were caused by faulty aseptic connections.

- 1.8 Environmental monitoring was increased on 17, 18, 19 and 20th of September, then returned to the previous level

Response to 1.8

Environmental monitoring was increased on 17-20th of September 2004 as part of the sterility investigation to confirm the effectiveness of the routine environmental monitoring regime and generate additional data in support of root cause determination. The knowledge generated from this exercise has been evaluated, and subsequent enhancements to the environmental monitoring programme were developed. The revised regime was presented during the MHRA inspection on 28-30 September 2004. This programme is being implemented.

2. Sterile Filtration Practices

- 2.1 Non-sterile MBP tanks taken into Grade ___ filtration area

Response to 2.1

We recognise that we are bringing non sterile bulk into the formulation suite for sterile filtration. The product is transferred into the formulation suite via written cleaning procedures, and handled within the suite in enclosed vessels in a controlled manner in accordance with written procedures.

Processing is designed to protect the open parts of the process (aseptic connections), whilst the environmental monitoring programme monitors the impact of the process on the environment.

- 2.2 Non-sterile bulk solution aerosol is vented through ___ filter from the non-sterile side of the filter into the grade ___ room in the ___ grade area. The ___ tubing was not securely attached to the vent valve prior to mid-September. The SOP for assembly of filter ___ does not require the fitting of vent filters.

Response to 2.2

The ___ µm filter ___ are vented into the grade ___ area to ___ filtration. The vent filters are ___ which

There is no evidence that aerosols of non-sterile bulk are vented through these filters.

There is no evidence that security of the tubing attachment was an issue. Based on a recommendation from MHRA during a previous inspection (13-14 September 2004) _____ were introduced.

Although the SOP did not specifically require the fitting of a vent filter, it was standard practice, and is verified within the manufacturing instruction to perform _____ filter integrity test (_____ the filters connected with the vessel. These filters (including the vent filter) are listed in the MI. The SOP will be updated to clarify the requirement for fitting of the vent filter.

2.3 Operators not dedicated to Grade _____ and Grade _____ ocation activities.

Response to 2.3

Within the Formulation Department, _____

1. _____ of MBP (non-sterile)
2. Sterile Filtration of MBP
3. Blending of Trivalent bulks

The rooms where these operations take place are all Grade _____ with localised Grade _____ areas for aseptic connections. Operators were dedicated to specific processes, but not specific tasks within those processes.

On completion of aseptic connections operators perform hand plate monitoring and subsequently change their outer gloves before performing any further activity. Operators perform frequent hand sanitisation with _____

To enhance sterility assurance the dedication of operators to Grade _____ and Grade _____ tasks within a specific process (eg sterile filtration) is being reviewed as part of our wider Quality System Improvement Plan (QSIP).

**2.4 Level of bioburden in some cases was at limit/exceeded _____
_____ cfu/ml). 12 monovalent blend pools (MBP) were
re-filtered as a result of being close to or exceeding the _____ bio-burden
limit.**

Response to 2.4

As the bioburden sample can only be taken immediately prior to filtration, the result is available following completion of the sterile filtration operation. A calculation is then performed. If the bioburden of the pre-filtered monoblend pool

exceeds _____ a refiltration is performed, in accordance with the approved SOP.

An NCR is raised each time a monoblend pool is refiltered as shown in the batch records and the NCR logs.

In addition, in house studies carried out using factory isolated *Serratia spp* in Fluvirin, have demonstrated that the _____ μm filter will retain a challenge _____ higher than the manufacturers stated: _____

- 2.5 **2 previous non-conformance reports for contamination (2002) of MBP recommended reducing the number of aseptic connections that have to be made during filtration. These changes have not been implemented.**

Response to 2.5

In relation to the 2002 non conformance reports, there is no documented evidence of a review of the number of aseptic connections having been carried out, however, discussions with staff involved indicate that a review was performed. Our understanding is that there was no scope for reducing the number of connections at that time.

As part of our continuous quality improvement in manufacturing technologies and GMP we are currently evaluating _____

_____. Also, as part of the site Quality Systems Improvement Programme (QSIP), a sterility assurance robustness programme has been initiated. A review of aseptic connections is within the scope of this programme.

3. **Scale up of production in 2004**

- 3.1 **Increase in egg inoculation from _____ % increase) Interim report indicates that there is an _____ : in processing time and a need for _____ to control bioburden**

Response to 3.1

A random sample of temperature data points taken across the 2003 and 2004 campaigns has been reviewed to confirm the recorded temperature of the harvested allantoic fluid. Although there is a slight _____ in processing time (approx _____ year on year, the actual temperature of the harvest fluid is no higher in 2004 (_____ C) than in 2003 (_____ C).

This is considered to have no significant impact in terms of process scale-up.

3.2 Increase in number of _____ machines from _____

Response to 3.2

This increase is in excess of the number of input eggs used within the process.

During the 2003 campaign, when a capacity increase from 2002 took place, additional centrifuges were installed to support the campaign. However these did not become fully operational until mid way through the campaign. The data demonstrates that the bioburden level remained constant throughout irrespective of the number of centrifuges utilised.

3.3 Increase in volume by _____ % of _____ from _____ but maintenance of _____ results in _____ of monovalent blend pools

Response to 3.3

The increased number of _____ processed by _____ necessitates: _____ The procedure requires _____ This _____ ratio is consistent across both 2003 and 2004. Nevertheless it is correct that the final _____ on completion of the _____ process has _____ Due to this, consideration has been given to the impact on sterile filtration parameters. In particular, the pre-filtered monovalent blend pool at _____ may lead to a _____

Process parameters have been reviewed and compared to what is considered as worst case for filtration using the _____. Based upon the review, the process parameters used for Fluvirin filtration do not approach worst case and it is considered that the scale-up of the process for 2004 has not had a detrimental effect on the filtration of the monovalent blend pools.

In 2004 we have specifically processed two batches at the 2003 scale (_____ eggs) the results from which confirm no significant impact on downstream processing due to the scale-up.

4. Breaches in Tank Integrity

4.1 An MBP tank was found to be leaking in 2003, the monovalent was transferred to a different tank and was not re-filtered. The finished product failed the sterility test.

Response to 4.1

The statement, as discussed during the close out meeting is incorrect, and should read: A trivalent tank was found to be leaking in 2003, the trivalent was transferred to a different tank and was not re-filtered. The finished product failed the sterility test.

The standard site practice for potential breaches of tank integrity is to assess each case individually. If the result of the assessment is that integrity has not been breached then contents are transferred as a precautionary measure. Environmental monitoring is carried out during the operation and sterility samples are taken before and after the transfer. An NCR is raised each time a tank transfer occurs. This particular incident is documented in NCR 2003/1874/03.

Re-filtration of trivalent product is not part of the validated process.

- 4.2 Tank integrity was breached in 2004 when the _____; was found to be loose, the bulk was transferred to a new tank without re-filtration.

Response to 4.2

This particular incident is covered by company NCR procedure. An NCR, which included assessment by Quality Management was completed. The investigation determined that whilst the _____ was loose, the actual _____; was secure, supported by data from a successful _____ test of the tank following product transfer. The data demonstrates that integrity of the tank was maintained.

Re-filtration of trivalent product is not part of the validated process.

- 4.3 Tank integrity was breached in 2004 when an _____ filter became detached, the filter was re-attached and the bulk was not re-filtered.

Response to 4.3

This particular incident relates to a trivalent batch and is covered by the company NCR procedure. An NCR, which included assessment by Quality Management was completed. The investigation determined that the integrity of the bulk was not compromised as the _____ ubing between the filter and tank was securely clamped.

Re-filtration of trivalent product is not part of the validated process.