



**Medicines and Healthcare products
Regulatory Agency**

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5th October 2004

Mr [REDACTED]
Chiron Vaccines Ltd
Gaskill Road
Speke
Liverpool
L24 9GR

Dear Mr [REDACTED]

**RE: Medicines Act 1968
Suspension of Manufacturer's Licence (ML18532/01) in relation to Influenza Vaccination Products**

I refer to the above manufacturer's licence granted to Chiron Vaccines Ltd, the investigative visits conducted by Mr P Hargreaves and Mr A J Hill on the 13th & 14th September 2004 and by Mr P Hargreaves and Mr I Rees between the 28th to 31st September 2004 at your manufacturing and assembly premises at Gaskill Road, Speke, Liverpool, L24 9GR and the representations made by your company (by email) on the 4th October 2004.

The Licensing Authority are, by this letter, exercising their powers under section 28 of the Medicines Act 1968 ("the Act") to suspend the above licence with immediate effect on the grounds that you have to a material extent contravened the provisions of the licence (see section 28 (4) (c)) by failing to conduct your operations in accordance with the principles and guidelines of Good Manufacturing Practice, (see paragraph 3 of Schedule 2 to the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971/972)). The suspension is limited to influenza vaccination products.

In view of the serious nature of the deficiencies identified as a consequence of the visits and the potential risk to public health if the products in question were to be released, it appears to the Licensing Authority that in the interests of safety it is necessary to suspend the manufacturer's licence (ML18532/01) in relation to all influenza vaccination products with immediate effect. In accordance with paragraph 11 of Schedule 2 of the Act, the licence is suspended with effect from 10:00a.m. on the 5th October 2004, for a period of three months.

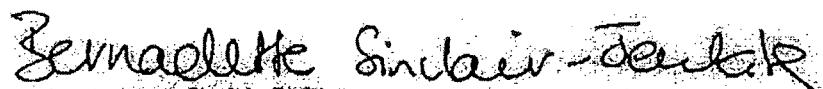
Manufacturing and assembly of any influenza vaccination products at your premises must cease immediately. The manufacture or assembly of medicinal products otherwise than in accordance with a licence is prohibited by section 45 of the Act. Any influenza vaccination products manufactured or assembled at the Gaskill Road site since 2nd March 2004 should be immediately quarantined and not released.

A list of the Inspectorate Findings during the 28th to 31st September 2004 investigative visit is appended at annex 1.



Please address any correspondence to the undersigned.

Yours sincerely



Mrs Bernadette Sinclair-Jenkins
A person authorised to sign on behalf of The Secretary of State for Health

Annex 1

2004 Flavirin Manufacturing Campaign - Inspectorate Findings

D R Hargreaves, I Rees
30th September 2004

General findings**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 5–8 incidents above — cfu/ml, whereas in 2004 the levels have been 10³ to 10⁷ with approximately 50 incidents to-date.
- 1.3 Non-conformance reports were only raised in June for bioburden levels in excess of — cfu/ml reported over the previous 3 months.
- 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 conclusion have yet been reached.
- 1.5 The number of instances of Gram negative organism contamination in a critical (sterile filtration) manufacturing room has increased significantly during 2004.
- 1.6 Organisms found in the bioburden are also found in the environment.
- 1.7 Organisms found in the bioburden have also been isolated from the sterile filtered monovalent bulk and from finished product (vials).
- 1.8 Environmental monitoring was increased on 17, 18, 19 and 20th of September, then returned to the previous level.

2. Sterile filtration practices:

- 2.1 Non-sterile monovalent blend pools (MBP) bulk tanks taken into grade — filtration area.
- 2.2 Non-sterile bulk solution aerosol is vented through — filters 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.
- 2.3 Operators are not dedicated to Grade — and Grade — operation activities.
- 2.4 The level of bioburden in some cases, was at the limit of or exceeded — cfu/ml). — MBP were re-filtered as a result of being close to or exceeding the — bioburden limit.

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

3 Scales up of production in 2004.

3.1 Increase in egg inoculation from _____ y' — b increase). Interim report indicates that there is an _____ in processing time and a need for _____ to control bioburden.

3.2 Increase in number of _____ machines from _____.

3.3 Increase in volume by _____ % of _____ from _____ but maintenance of _____ results in increased _____.

4 Breaches in tank integrity.

4.1 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.

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

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