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DEPARTMENT OF COMMUNITY SERVICES AND HEALTH

3

86/9010
February 2, 1993

The Director
TGA Laboratories

APPLICATION FOR REGISTRATION

PRODUCT: "TARGOCID INJECTION" TEICOPLANIN,
100 MG IN 5 ML VIAL PLUS WFI IN 1.9 ML AMPOULE
200 MG IN 10 ML VIAL PLUS WFI IN 3.2 ML AMPOULE
400 MG IN 20 ML VIAL PLUS WFI IN 3.2 ML AMPOULE
MANUFACTURER: GRUPPO LEPETIT, ANAGNI, ITALY
APPLICANT: MERRELL DOW PHARMACEUTICALS, NORTH SYDNEY

Evaluation of Company Responses

The company has now responded to questions that were raised in the departmental letter of August 25, 1992 (f.136-142). The numbering of this letter is retained in this evaluation:

12. Sterility matters:

12.1 The company has supplied a copy of Method Number B211800 as requested. This document contains details of room and equipment preparation and basic details of the membrane filtration method for sterility testing.

12.2 The company has stated that the methods used for the 100 mg and 400 mg vials of powder are the same as that used for the 200 mg vials. The method has been validated for each weight. This is acceptable.

12.3 to 12.6

Responses to these 4 questions have not been provided at this time. In a general comment, the company has stated that additional information will be forwarded once it has been received from their overseas subsidiaries.

It is noted that Section 5 of document B211800 contains details of interpretation of sterility test results. It is not clear however, whether this specifically relates to testing of the vials of Teicoplanin Powder or to the ampoules of WFI. In the previous sterility evaluation of November 7, 1991, (f.97-99) this document was mentioned in relation to testing of the Teicoplanin Powder.

According to document B211800, the sterility test is repeated if contamination is detected in the First Test. If the First Test cannot be invalidated a Repeat Test is performed using twice the number of units tested in the First Test. The Repeat Test may be invalidated depending upon the outcome of an investigation into manufacturing controls and testing procedure. This interpretation is not acceptable as it appears to include provisions for repeated testing which may lead to a contaminated batch being accepted.

In their B1 data the company stated that the WFI must comply with the Ph Eur specifications for WFI. They were then informed of the reasons as to why the interpretation of the sterility test in the EP was unacceptable (Q12.6). Unfortunately, the paragraph explaining the interpretation of sterility test results in the Australian Code of GMP, Appendix C, appears to have been inadvertently omitted from the departmental letter (f.137 & 97). In view of this omission and the fact that the Teicoplanin Powder test is validated in accordance with the USP XXII the company should be informed of the requirements of Appendix C in relation to sterility test interpretation.

NB. Regarding labelling:

The product labels attached to f.104 are labels for the UK product which were forwarded to the TGAL Antibiotics Section by the National Institute for Biological Standards and Control, UK, in response to the letter on f.101. The UK labels do not contain a warning regarding the absence of antimicrobials.

Copies of Australian labels as supplied in Appendix 9 (f.147, Q14) do actually state the following, "contains no antimicrobial agent, use once only and discard the residue". This is acceptable.

RECOMMENDATIONS

The following matters should be raised with the company and satisfactory replies received before approval is granted for Registration of "Targocid Injections":

12.3.to 12.6

When available, these responses should be forwarded for evaluation.

In regard to Q12.6 you have already been informed that the interpretation of sterility test results in the EP is not satisfactory. Furthermore:

a) You should also be aware that the interpretation of results of the sterility test in the USP is not

acceptable as it is considered to be very loosely defined. If contamination is detected in the first stage test the test may be declared invalid if a review of the sterility testing facility of the monitoring, materials used, testing procedure and negative controls indicates that faulty technique was used in the test. Invalid tests may be repeated and there appears to be no barrier to the first stage test being undertaken several times.

Similarly the second stage test may be declared invalid and repeated.

The repeated testing permitted could lead to contaminated batches being accepted.

b) If tests are performed competently in a clean environment the chance of adventitious contamination occurring in both the original test and the repeat test is negligible. Provisions which may permit repeated retesting should not be necessary.

c) It is suggested that if contamination is detected in a test then a retest should be carried out using double the number of test units. Negative controls should be tested concurrently. If contamination is detected in the retest then the batch should be rejected unless contamination in the controls indicates that the test was invalid. If the test is invalid it may be repeated. This paragraph was inadvertently omitted from Q12.6 in the departmental letter of August 25, 1992.

d) You should confirm that the interpretation in (c) above will be adopted for both the vials of Teicoplanin Powder and the ampoules of WFI. Alternatively you may provide an assurance that vials of Teicoplanin Powder and ampoules of WFI destined for Australia will be selected from batches which pass the first test.

[redacted]