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DEPARTMENT OF COMMUNITY SERVICES AND HEALTH

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86/09010
7 November 1991

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
SPONSOR	:	MERRELL DOW PHARMACEUTICALS, NORTH SYDNEY

EVALUATION OF STERILITY ASPECTS

The product is an antibiotic bactericidal to Gram positive organisms. It is presented as a lyophilised powder in a glass vial with butyl rubber stopper and aluminium ring seal together with a glass ampoule of Water for Injections (Ph Eur). The 100 mg vial is presented with a 1.9 mL ampoule and the 200 and 400 mg vials with a 3.2 mL ampoule.

The labels are acceptable from a microbiological viewpoint. Both vial and carton label state "contains no antimicrobial agent, use only once and discard the residue".

The carton labels state that the prepared solution may be injected directly or added to a suitable infusion solution. There is no added preservative in either powder or WFI. The product information dosage and administration instructions state that prepared solutions diluted with peritoneal dialysis solutions containing 1.36% or 3.86% dextrose should be discarded after 24 hours. This is acceptable.

Sterile Manufacture

Acceptable documentary evidence has been provided relating to the standard of the manufacturer (f 96).

Sterility Testing

A sterility test is part of batch release specifications for both vials of powder and ampoules of Water for Injections.

Some details of the sterility test method and validation have been provided for the 200 mg vials. The contents of 20 vials are dissolved in 400 mL of diluent D (not identified, presumably as in USP XXII) and filtered through a 2 unit Millipore Steritest AB system. The membranes are washed 20 times with 100 ml of 1% bovine serum albumin in Diluent D, and 4 times with 100 ml of Diluent A (presumably as in USP XXII). Media used are Fluid Thioglycollate and Trypticase Soy Broth. The incubation period is 14 days. In the validation the temperatures used were 30-35° for the FTG and 20-25° for the TSB. Room preparation, equipment and incubation of the Millipore units are described in method B211800, which was not provided.

The method was validated in accordance with the USP XXII and BP 88. Details are satisfactory. Results provided indicate that growth of the challenge organisms occurred within 2 days. Media used in the validation was tested for sterility and fertility and presumably is tested routinely.

There are no details of the method used for the 100 or 400 mg vials; if it is the same as for the 200 mg vials confirmation should be sought that it has been validated for each weight.

There are no details of the method of testing the ampoules of Water for Injections. The specifications simply state that they must conform to the Ph Eur specifications for Water for Injections.

There is no mention of stasis testing, the use of negative controls and no statement regarding interpretation of results.

Recommendations

The following points should be put to the company regarding sterility testing:-

1. Reference is made to Method B211800 in B1 Volume 1 P 120 and B1 Vol 2 P 395 (Appendix 14). This method was not provided. Please supply a copy.

2. No details of the methods used for the 100 or 400 mg vials of powder have been provided. If they are the same as for the 200 mg vials please confirm that the method has been validated for each weight. If not the same, please provide details.

3. Additional details of sterility testing of the ampoules of Water for Injection are required. The European Pharmacopoeia is not sufficiently specific. Please state the number tested from each batch, if the whole contents of each ampoule is tested, if the method used is membrane filtration and if the incubation period is 14 days.

4. Please provide evidence to demonstrate that the sterility test media, in the presence of the product, will support the growth

of low numbers of viable challenge organisms added at the end of the sterility test incubation period.

5. Please describe the type and number of simulated negative controls used in the sterility test of both powder and Water for Injection (see Australian Code of GMP for Therapeutic Goods, section C450).

6. You have not provided information regarding the interpretation of sterility test results. If the interpretation is in accordance with the European Pharmacopoeia, you should be aware that TGAL considers that the interpretation in the European Pharmacopoeia is not satisfactory. The provision made for a second retest is not acceptable as it allows too high a probability that a contaminated batch will be accepted. If the 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. Provision for a second repeat test should not be necessary.

   It is difficult to prove the identity of two isolates. Furthermore, a contaminated batch may well contain more than one type of microorganism. Therefore lack of identity of isolates is not an adequate reason for permitting a second repeat sterility test.

   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 was invalid it may be repeated.

   You should confirm that this interpretation will be adopted or, alternatively, provide an assurance that product for Australia (both teicoplanin powder and Water for Injection) will be selected from batches which pass the first test.

Approval for registration should not be granted until a satisfactory response to these points has been received.

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Microbiology

[redacted]

Computer updated
cln 91.156.2.

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