197

File No: 86/9010
App No: 91/156/2
Eval No: a030
EVAL:FN

FILE NOTE

APPLICATION FOR REGISTRATION
TEICOPLANIN
'TARGOCID' POWDER FOR INJECTION IN VIALS
100, 200 AND 400 mg PLUS WATER FOR INJECTION
MARION MERRELL DOW AUSTRALIA PTY LTD

Correspondence: Company letters of 12 March 1991, 29 July 1991, and 12 September 1992. Company reply of 1 December 1992 to TGA's letter of 25 August 1992.

EVALUATION OF COMPANY RESPONSES

MANUFACTURE OF RAW MATERIAL TEICOPLANIN

MANUFACTURING FACILITIES

1. The standard of GMP is acceptable (see folio 164).

ACCEPTABLE

2. Dedicated equipment is used exclusively for the production of teicoplanin at the Brindisi facility. Although it should be noted that rifampicin is also produced at the same site.

ACCEPTABLE

3. The crude fermentation product is no longer transported to the Lepetit Research Centre in Milan. All steps are now performed a the Brindisi plant.

ACCEPTABLE

4. THE PRODUCING ORGANISM

Strain improvement procedures are still at the experimental stage, and are ongoing. No change of strain has been finalised or implemented as far as commercial production is concerned.

ACCEPTABLE

5. IN-PROCESS CONTROLS

a) Microbial and fungal contamination. Individual colonies are examined microscopically before preculture (the 300-700L stage). If any contamination is detected the batch is destroyed. At later stages mycelial growth in the fermentation broth is monitored as well as the teicoplanin content. On detection of any contamination the entire batch is destroyed. All vessels are cleaned and the cause is investigated with the aim of rectifying the problem.

ACCEPTABLE

b) The company has provided a brief description of reprocessing that is carried out in the event of batch failure where the A3 component or sodium chloride exceeds the specified limits. The logic of the process is outlined in Appendix 1. The attachments

shows analytical results from 23 batches made by the current process. Residual acetone levels range from 0.1 to 1.0% with a mean of 0.6%. The company has also provided results for 10 batches made by the research process. The residual acetone ranges from >0.01 to 4.7% and that for butanol 0.3 to 3.0%. The original raw material specifications (see f 119) show limits of NMT 1% for acetone and NMT 0.1% w/w for butanol.

ACCEPTABLE

6 ACTIVE INGREDIENT

6.1 One microgram of teicoplanin activity potency is defined as the activity contained in 1 microgram of teicoplanin in the teicoplanin master standard.

The International Standard (Biologicals 1991, 19, 233-236) contains 1 mg by weight teicoplanin A2 group equivalent to 1000 Units of biological activity. The conversion applied to the A3 group is based on molecular weights of 1884 for the A2 group and 1564 for the A3 group and is A3/A2 or 0.83.

ACCEPTABLE

6.2 From the references quoted (see Appendix 2) some idea of the differential antibacterial activity of teicoplanin components is evident. The relative rating of each component depends on the target organism. The MIC values quoted are in terms of μg/mL (or mg/L) and would need to be corrected for molecular weight to give true specific activities. It should be noted that the aglycone (no sugars) is quite active. In general the teicoplanin A2 group is more active than the T-A-3-1 component.

ACCEPTABLE

7. RAW MATERIAL SPECIFICATIONS

7.1 Teicoplanin Assay

The company proposes that the potency of the raw material be expressed in terms of μg activity/mg according to the reasoning expressed in 6.1 above. This is acceptable. It was proposed that the company follow the model of the BP Vancomycin monograph. The response shows that the company is somewhat confused by the cocept of fiducial limits. The proposed release limits of a lower fiducial limit of not less than 900 μg/mg is acceptable.

ACCEPTABLE

7.2 Composition

[redacted]

[redacted]

TO BE RESOLVED

7.3 Water Content

a) The company makes the statement that a reduction of the moisture content increases the percentage of the A3 component and

refers to Attachment 6.

However, data given in table I.A.5.1 do not support this statement (see Appendix 3 of this report). Indeed there is no significant relationship between initial moisture content and initial A3 content. Furthermore during development of the manufacturing process it was discovered that removal of water below 5% is very difficult and ultimately gave a drug of higher A3 content.

b) A drum drying process is used and the lowest amount of water that can be achieved is quoted at 10-12%. More severe drying (the same equipment is implied) causes hydrolysis. Batch data provided by the company, in contrast show moisture contents between 5.3 and 13.0% without a detrimental effect on the bulk substance.

Therefore the proposed 15% water content limit would appear to be too generous and should be lowered to 12%. My impression is that the drying process is not very well controlled hence the wide range of moisture contents.

TO BE RESOLVED

8. RECENT BATCH ANALYSIS

The company has submitted data for 3 batches of teicoplanin bulk substance in the form of Certificates of Analysis.

Batch 0060 manufactured 27/7/90
Batch 0061 manufactured 20/3/90
Batch 0062 manufactured 19/2/90

The quality of the batches is satisfactory.

ACCEPTABLE

9. STABILITY STUDIES

9.1 The company has also provided 24 months stability data for the same three batches referred to in 8. of this report.

The batches were monitored for teicoplanin content (microbiological assay and HPLC assay) and for the relative proportions of A3 and A2 components. The last test description is impossible to read and the company should be asked to explain what it is. Although requested the company replied that water content was not considered an important parameter and is therefore not monitored in these stability studies. This is a little short sighted as the company specification calls for microbiological assay corrected for water, NaCl, solvents and inorganics, see certificates of analysis. It is therefore impossible to interpret assay results in absolute terms. At best they represent an 'as is' basis.

The company should be asked for comment.

[redacted]

TO BE RESOLVED

9.2 The company has provided initial water contents of the

requested batches (f.151). All are within an acceptable range 9.1-10.9%.

ACCEPTABLE

9.3 So far few batches have required reprocessing, a procedure which involves n-butanol.

The company states that these batches do not differ from those that have not been reprocessed with butanol.

ACCEPTABLE

FORMULATION AND MANUFACTURE

[redacted]

The company's explanation should be accepted. However, for regulatory purposes the pharmacopoeial approach of total vial contents will be followed.

The question of a stable foam will be dealt with when reconstitution instructions are discussed under 14. LABELLING MATTERS.

The question of fiducial limits will be dealt within 11.3.

The justification is ACCEPTABLE

10.2 The company has provided an explanation of the reconstituted concentration of teicoplanin (see 10.1)

ACCEPTABLE

10.3 The company has acknowledged an error in the original documentation and has confirmed that microbiological assessment (not HPLC) is used to determine the potency of the teicoplanin raw material. The company has assured the department that all documents affected by this error have been changed.

ACCEPTABLE

[redacted]

ACCEPTABLE

11. SPECIFICATIONS FOR THE FINISHED PRODUCTS

11.1 The expiry specifications are identical to the release specifications. This statement is contradicted with respect to the Teicoplanin assay (see 11.3) so presumably applies to all other specification tests.

ACCEPTABLE

11.2 The company states that vials are freeze dried to a water content of less than 1.5% w/w to assure that the product will not go beyond 2.5% w/w. This is understandable but the next leap in logic is unclear. "This is normal variation between batches since it is first dried by LOD in-process then analysed by Karl Fischer to meet the specification of NMT 2.5%."
Where the LOD is involved is not evident since only the Karl Fischer method is used to determine water content (see specifications).

The company should be asked for an explanation.

TO BE RESOLVED

11.3 (a, b) The company have given satisfactory assurances with respect to statement of teicoplanin activity in the finished products and the reference substance (see also 6.1 ad 7.1 this report).

ACCEPTABLE

11.3 (c) The company originally proposed two tests for the content of active. One was based on the entire vial contents, the other was based on the extractable volume.

TGA in their letter of 25 August 1992 stated that for Australian purposes assay results based on the entire vial content will be used.

The company has re-affirmed the original specification where two types of tests are carried out. A microbiological assay related to the entire vial content and the total volume of vial contents when reconstituted is acceptable. The matter of the other test based on extractable volume will be raised in the discussion of Fiducial limits (see 11.3 (d)).

ACCEPTABLE

11.3 (d) The company has provided fiducial limits for the microbiological assay of the active at release and expiry:

Presentation (overage %)	**Release**	**Expiry**
200 mg vials (10%)	LFLE NLT 95% UFLE NGT 115%	LFLE NGT 120% UFLE NLT 95%
400 mg vials (15%)	LFLE NLT 95% UFLE NGT 115%	LFLE NGT 120% UFLE NLT 95%
100 mg vials (25%)	LFLE NLT 95% UFLE NGT 130%	LFLE NGT 130% UFLE NLT 95%

These are not acceptable.

In view of the overages for the total vial contents, the limits should be:

Presentation (overge %)	**Release**	**Expiry**
100 mg vials (25%)	LFLE NLT 95% UFLE NGT 130%	LFLE NGT 130% UFLE NLT 95%
200 mg vials (10%)	LFLE NLT 95% UFLE NGT 115%	LFLE NGT 115% UFLE NLT 95%
400 mg vials (15%)	LFLE NLT 95% UFLE NGT 120%	LFLE NGT 120% UFLE NLT 95%

These same limits are not appropriate for the extractable volume assay. The assay results based on the extractable volume test in view of the possible variations (see point 10.1 above) is not a viable QC test.

These matters should be raised with the company.

The release and expiry limits for the A3 versus the A2 components of the complex are the same for all presentations as follows:

[redacted]

MATTERS TO BE RESOLVED

12. STERILITY

These have been evaluated separately by the sterility evaluator (ff.183 to 181).
There are outstanding matters to be raised with the company.

TO BE RESOLVED

13. SAFETY TESTS

These have been evaluated separately by the pharmacology evaluator (f.172). There remain outstanding matters to be resolved.

TO BE RESOLVED

14. LABELLING MATTERS

The company has adopted the department's suggestions.

14.1 The label now reflects the vial content of active substance in terms of total international units of activity.

ACCEPTABLE

14.2 The company has altered the labels as suggested with respect to name of goods and route of administration.

ACCEPTABLE

14.3 & 14.6 The company has removed the details about concentration of active in the reconstituted solution from the container and carton labels. This would be more appropriate in the product information leaflet. The company accepts this.

In view of the special care and precautions required to prevent foaming during the reconstitution procedure it would be appropriate to have a special warning statement on the carton and vial labels. (see 14.6 responses as well) 'WARNING SPECIAL RECONSTITUTION PROCEDURES APPLY'. A clear description of the procedure as a leaflet separate from the Product Information would be preferable, entitled PROCEDURE FOR RECONSTITUTION.

TO BE RESOLVED

14.4 The ambiguous 'dilute before use' statement has been removed as requested.

ACCEPTABLE

14.5 The company has altered the reconstitution instructions for the cartons for all three presentations and 400 mg presentation vial.

ACCEPTABLE

14.6 The company has justified the DO NOT SHAKE STATEMENT.

The attention of the MSA should be drawn to the fact that this preparation if over shaken has a strong tendency to form a stable

foam. This can give problems in the withdrawal for a dose for injection (iv or im).

ATTENTION OF MSA

14.7 The carton label now clearly indicates that it contains one vial of teicoplanin powder and one ampoule of diluent (water for injection).

ACCEPTABLE

RECOMMENDATIONS

Several matters still remain to be resolved.

The same points as were made in the original evaluation should be drawn to the attention of the MSA together with the tendency of the reconstituted solution to foam.

The approval for registration is not recommended until the matters raised with the company have been resolved.

[redacted]

Antibiotics Section
TGAL

8 February 1993

[redacted]

REPROCESSING OF TEICOPLANIN

18

[redacted]

APPENDIX 2

Table 8. *In vitro* antibacterial activity.

Organism	MIC (μg/ml)			
	Teicoplanin	T-A3-1	T-A3-2	T-Aglycone
Staphylococcus aureus ATCC 6538	0.1	0.4	0.2	0.25
S. aureus Tour	0.4	0.4	0.2	0.05
S. aureus Tour[a)]	0.8	1.6	0.8	0.2
S. aureus Tour[b)]	0.8	0.8	0.4	0.4
S. epidermidis ATCC 12228	0.4	0.4	0.05	0.0125
Streptococcus pyogenes C203	0.05	1.6	1.6	0.05
S. pneumoniae UC41	0.05	1.6	1.6	0.05
S. faecalis ATCC 7080	0.2	1.6	0.8	0.1
Escherichia coli SKF 12140	>800	>800	>800	25
Proteus vulgaris X 19 H ATCC 881	>100	>100	>100	50
Pseudomonas aeruginosa ATCC 10145	>100	>100	>100	>100

a) Inoculum 10^4 cfu/ml.
b) Determined in the presence of 30% bovine serum.

Malabarba et al (1984)

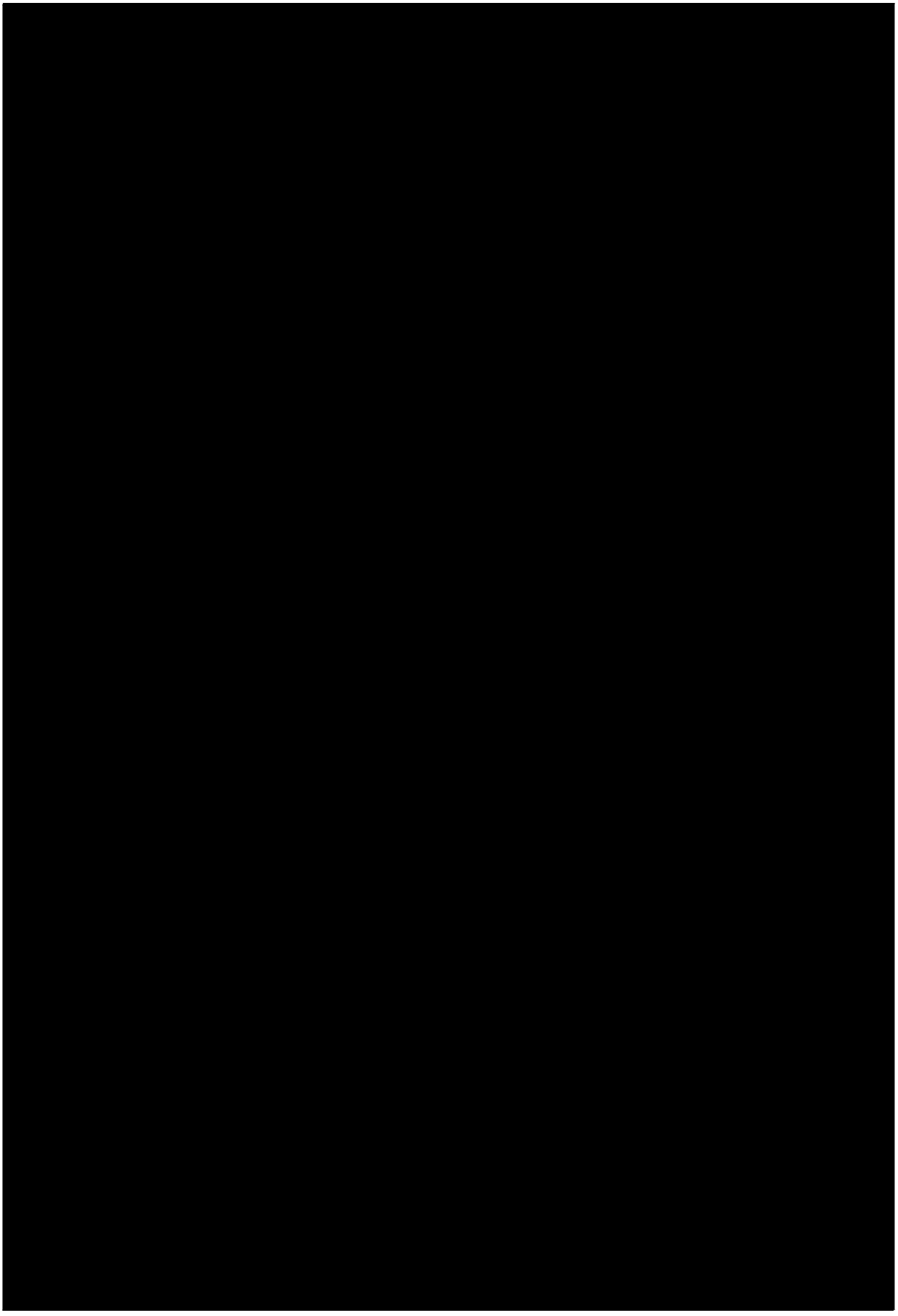
TABLE VI

Antibacterial activity and association constants with Ac-D-Ala-D-Ala of acid and basic hydrolysis products.

Compound	MIC (mg/l) (a)						K_A (b) ($l\ mol^{-1}$)
	Staph. aureus	*Staph. haemolyticus*	*Staph. epidermidis*	*Strept. pyogenes*	*Strept. pneumoniae*	*Strept. faecalis*	
Teicoplanin	0.125	4.0	0.125	0.06	0.06	0.06	$1.18 10^8$
T-A3-1	0.25	8.0	0.25	0.5	0.5	2.0	$1.2 10^8$
T-A3-2	0.5	0.5	0.125	0.5	1.0	1.0	$1.0\ 10^8$
T-aglycone	0.063	0.25	0.016	0.125	0.125	0.125	$4.0\ 10^5$
epi-teicoplanin	12.5	nd	12.5	3.2	12.5	25.0	nd

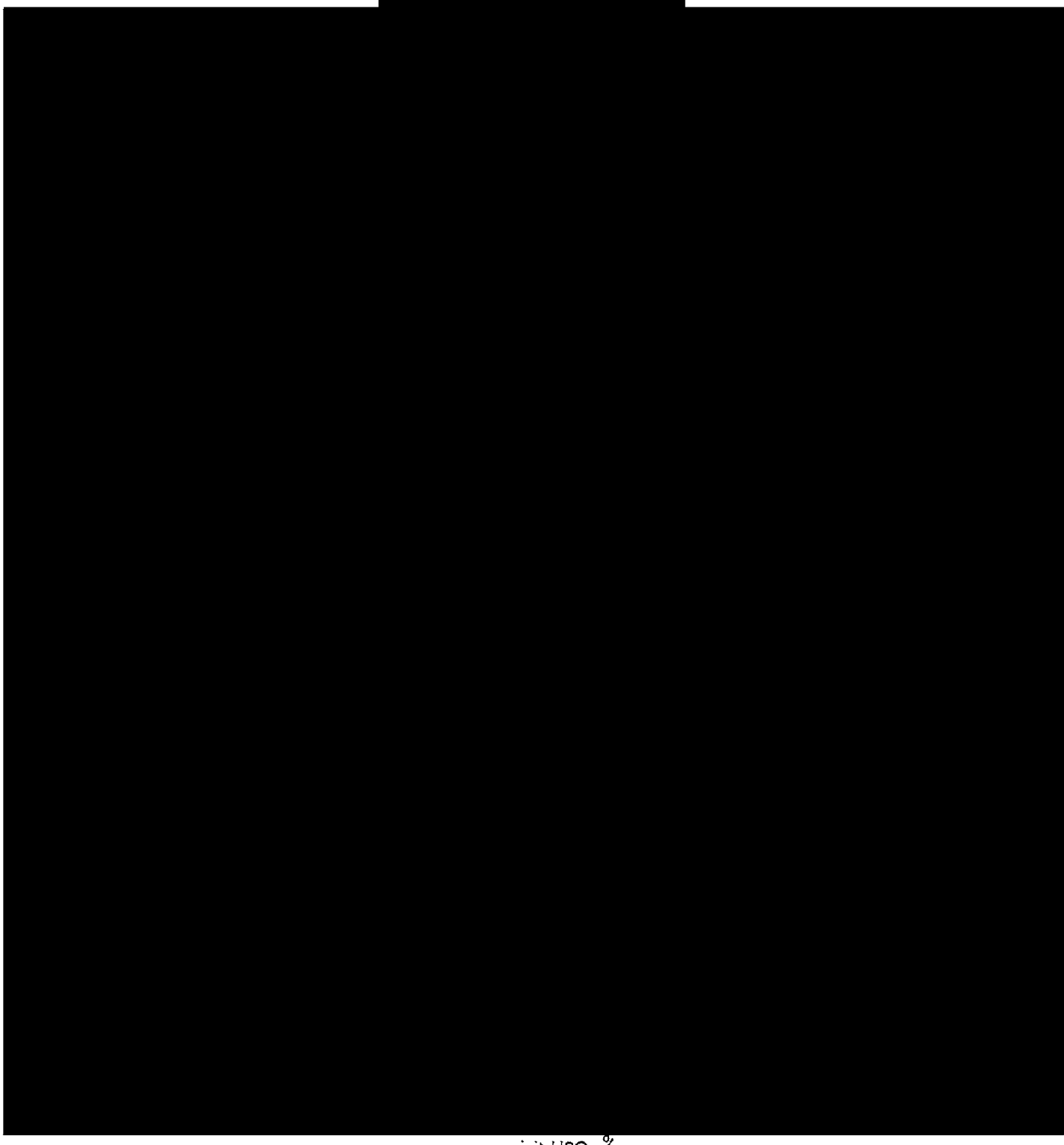
(a) See Table 5.
(b) Measured by UV difference spectroscopy in 0.02 M citrate at pH 5.0. Derived from Ref. 25.
nd = not determined

Coronelli et al, Il FARMACO Ed. Sc., Vol. 42, (No. 10), p782



APPENDIX 3

TEICOPLANIN



init H2O %

APPENDIX 3

TEICOPLANIN

[redacted]