DRAFT REVISIONS FOR COMMENTS

This draft revision contains revised monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to further revisions prior to publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in before the last date for comments.

Document History and Schedule for the Adoption Process

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Further follow-up action as required.	

1. **Effectiveness of Antimicrobial Effectiveness (2.2.2.)** Vol I, Page 33

Under Procedure.

Change From: Inoculate each container with one of the prepared and standardized inoculum in such a way that after inoculation the final concentration of the organisms remains between 1×10^5 and 1×10^6 CFU per ml and the volume of the inoculum does not exceed 1 per cent of the volume of the product. The initial concentration of the viable organisms in each test preparation is estimated based on the concentration of the microorganisms in each of the standardized inoculum as determined by the pour plate method or membrane filtration method.

To: Inoculate each container with one of the prepared and standardized inoculum in such a way that after inoculation the final concentration of the organisms remains between 1×10^5 and 1×10^6 CFU per ml. For antacids made with aqueous base, the final concentration of the test preparation after inoculation is between 1×10^3 and 1×10^4 cfu/ml of the product. The volume of the inoculum does not exceed 1 per cent of the volume of the product. The initial concentration of the viable organisms in each test preparation is estimated based on the concentration of the microorganisms in each of the standardized inoculum as determined by the pour plate method or membrane filtration method.

2. **Guidelines on Bacterial Endotoxin Tests (2.2.33)** Vol I, Page 163

Section 5. Alternate Test Method. Change to:

The methods mentioned in *Bacterial Endotoxin* (2.2.3.) for the detection of bacterial endotoxins (Gel-clot limits test, semi quantitative gel-clot, kinetic turbidimetric, kinetic chromogenic and endpoint chromogenic) are considered to be validated. However, a laboratory may choose to use an alternative method that is not mentioned in *Bacterial Endotoxin* (2.2.3.), for example Recombinant Factor C (rFC) or Recombinant Cascade Reagents (rCR). If such a choice is made, the alternate test for the detection of bacterial endotoxins must be fully validated to ensure that decisions made using the alternate methodology are equivalent to or better than decisions made using the validated pharmacopoeial methods and ultimately approved by the appropriate regulatory authority.

3. **Biological Indicator (5.2)** Vol I, Page 1289

Section 9. Ionizaing Radiation Sterilizing Process. Line 8

Change From: It has a labelled spore count of not less than 1.0×10^7.

To: It has a labelled spore count of not less than 1.0×10^6.

4. **Lactulose Solution.** Vol II, Page 3045

Microbial Contamination (2.2.9)

Change From: Total microbial count is not more than 10^2 CFU per g of lactulose. 1 g is free from Escherichia coli and 10 g is free from Salmonella.

To: Total microbial count is not more than 10^2 CFU per ml of lactulose. 1 ml is free from Escherichia coli and 10 ml is free from Salmonella and Shigella.

5. **Desferrioxamine Mesylate.** Vol II, Page No. 2317

Bacterial Endotoxins (2.2.3)

Change From: Not more than 0.025 Endotoxins Units per mg of desferrioxamine.

To: Not more than 0.33 Endotoxins Units per mg of deferoxamine mesylate.

6. **Desferrioxamine for Injection.** Vol II, Page No. 2318

Bacterial Endotoxins (2.2.3)

Change From: Not more than 0.025 Endotoxins Units per mg of desferrioxamine.

To: Not more than 0.33 Endotoxins Units per mg of deferoxamine mesylate.

7. **Water for Injection.** Vol III, Page No. 4480

Under Tests. Microbial contamination (2.2.9).

Change From: Total viable count not more than 10 CFU per 100 ml and free from specified microorganisms.

To: Microbial monitoring. During production and subsequent storage, appropriate measures are taken to ensure that the microbial count is adequately controlled and monitored. Appropriate alert and action levels are set so as to detect adverse trends. Under normal conditions, an appropriate action level is a microbial count of 10 CFU per 100 ml when determined by filtration through a membrane with a nominal pore size not greater than 0.45 µm, using R2A Agar, using at least 200 ml of water for injections in bulk and incubating at 30-35 °C for not less than 5 days. For aseptic processing, stricter alert levels may need to be applied. Specified micro-organisms should be absent.

Medium. Reasoner's 2A Agar

Yeast extract	0.5 g
Proteose peptone	0.5 g
Casein hydrolysate	0.5 g
Glucose	0.5 g
Starch	0.5 g

Dipotassium hydrogen phosphate	0.3 g
Magnesium sulfate, anhydrous	0.024 g
Sodium pyruvate	0.3 g
Agar	15.0 g
Purified Water	1000 ml

Adjust the pH so that after sterilisation it is 7.2 ± 0.2. Sterilise by heating in an autoclave at 121° for 15 minutes.

Method - Growth promotion of R2A agar.

- ***Preparation of test strains.*** Use standardised stable suspensions of test strains or prepare them as stated in Table 1. Seed lot culture maintenance techniques (seed-lot systems) are used so that the viable micro-organisms used for inoculation are not more than 5 passages removed from the original master seed-lot. Grow each of the bacterial strains separately as described in Table 1. Use buffered sodium chloride-peptone solution pH 7.0 or phosphate buffer solution pH 7.2 to make test suspensions. Use the suspensions within 2 hours, or within 24 hours if stored at 2° to 8°. As an alternative to preparing and then diluting a fresh suspension of vegetative cells of Bacillus subtilis, a stable spore suspension is prepared and then an appropriate volume of the spore suspension is used for test inoculation. The stable spore suspension may be maintained at 2° to 8° for a validated period of time.
- ***Growth Promotions.*** Test each batch of ready-prepared medium and each batch of medium, prepared either from dehydrated medium or from the ingredients described. Inoculate plates of Reasoner's 2A agar separately with a small number (not more than 100 CFU) of the micro-organisms indicated in Table 1. Incubate under the conditions described in the table. Growth obtained must not differ by a factor greater than two from the calculated value for a standardised inoculum. For a freshly prepared inoculum, growth of the micro-organisms must be comparable to that obtained with a previously tested and approved batch of medium.

Table 1: Growth Promotion of Reasoner's 2A Agar

Micro-organism	Preparation of the test strain	Growth Promotion
Pseudomonas aeruginosa such as: *ATCC 9027* *NCIMB 8626* CIP 82. 118 NBRC 13275	Casein soyabean digest agar or casein soyabean digest broth 30°-35° 18-24 hours	Reasoner's 2A agar ≤ 100 CFU 30°-35° ≤ 3 days
Bacillus subtilis such as: ATCC 6633 NCIMB 8054 CIP 52.62 NBRC 3134	Casein soyabean digest agar or casein soyabean digest broth 30° -35° 18-24 hours	Reasoner's 2A agar ≤ 100 CFU 30°-35° ≤ 3 days