PHARMACY AND POISONS BOARD
OF HONG KONG

Requirement of Microbiological Quality of Registered Pharmaceutical Products in Non-sterile Dosage Forms

Background

Under the Pharmacy and Poisons Ordinance (Cap. 138) and its Regulations (Cap. 138A), pharmaceutical products should meet the criteria of safety, efficacy and quality, and be registered with the Pharmacy and Poisons Board before they can be sold in Hong Kong.

2. The presence of certain micro-organisms in non-sterile preparations may reduce or inactivate the therapeutic activity of the products thus imposing potential risks to patients. Therefore, microbiological limit of pharmaceutical products in non-sterile dosage forms should be controlled.

3. Microbiological examination of pharmaceutical products in non-sterile dosage forms has been included in various pharmacopoeias, such as US Pharmacopoeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (EP) and Japanese Pharmacopoeia (JP), etc. In May 2009, the microbiological requirement was harmonised in the above pharmacopoeias.

Registration Requirement

4. To ensure the safety and quality of registered pharmaceutical product in terms of microbiological quality, the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances : Certification of Clinical Trial / Medicinal Test) Committee (the Committee) decided that, **with effect from 1 October 2019**, all registered pharmaceutical products (which include pharmaceutical products under application and existing registered pharmaceutical products) in non-sterile dosage forms, throughout their shelf life, should meet the harmonised acceptance criteria for microbiological quality as specified in the various major pharmacopoeias specified in paragraph 3 and is extracted in Table 1 below:

Table 1: Acceptance Criteria for Microbiological Quality of Non-sterile Dosage Forms

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
Nonaqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli* (1 g or 1 mL)
Rectal use	10^3	10^2	—
Oromucosal use Gingival use Cutaneous use Nasal use Auricular use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or1 mL)
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch) Absence of *Pseudomonas aeruginosa* (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulization)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of bile-tolerant Gram-negative bacteria (1 g or 1 mL)

Remarks:

The methods for microbial examination of non-sterile products should take reference from USP, BP, EP or JP.

Acceptance criteria are based on individual results or on the average of replicate counts when replicate counts are performed (e.g., direct plating methods). When an acceptance criterion for microbiological quality is prescribed, it is interpreted as follows:

10^1 cfu: maximum acceptable count = 20;
10^2 cfu: maximum acceptable count = 200;
10^3 cfu: maximum acceptable count = 2000; and so forth.

Reference: BP Appendix XVI D. Microbiological Quality of Non-sterile Pharmaceutical Preparations and Substances for Pharmaceutical Use; Ph. Eur. General Text 5.1.4

5. Accordingly, the registration certificate holders are required to comply with the aforementioned requirements of microbiological quality of pharmaceutical products

in non-sterile dosage forms. For registered pharmaceutical products found to exceed the specified acceptance criteria for microbiological quality, the registration certificate holders are required to provide evidence that the product manufacturer has conducted appropriate root cause analysis and adopted corrective and preventative actions to the Drug Office for assessment. If the root cause analysis or evidence to adopt appropriate corrective and preventive actions are found to be unsatisfactory, the case would be brought up to the Committee for consideration; and the concerned pharmaceutical product may subject to deregistration, suspension of registration for a specified period of time or a warning letter will be issued to the registration certificate holder in accordance with Regulation 36(8) of Pharmacy and Poisons Regulations (Cap. 138A) if the Committee considers it to be in the public interest to do so.

6. The microbiological quality acceptance criteria are subject to revision and updates in the pharmacopoeias. In case any discrepancies or inconsistencies of the acceptance criteria between Table 1 and the pharmacopoeias, the latest version of the aforementioned pharmacopoeias shall prevail.

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