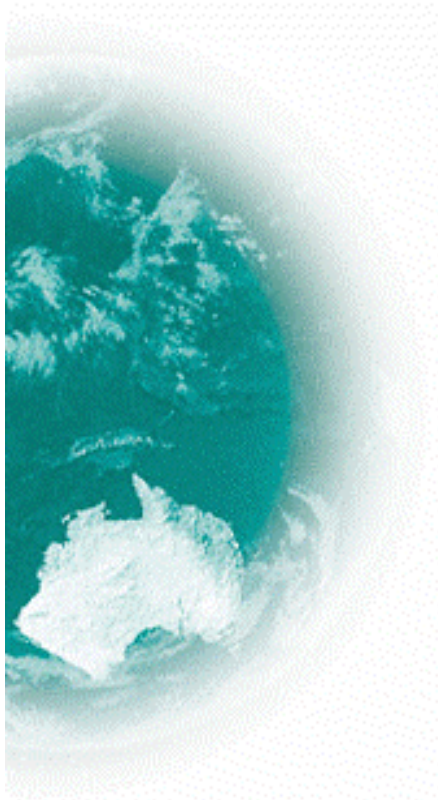




Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Prescription Medicines



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APPENDIX 16: PRESERVATIVE EFFICACY TESTING

Sponsors should note that Preservative Efficacy Testing should be conducted in accordance with the relevant British Pharmacopoeia (BP) monograph.

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Appendix 14 (*Stability Testing*) and the Committee for Medicinal Products for Human Use (CHMP) *Note for Guidance on Stability Testing of New Drug Substances and Products* (CPMP/ICH/2736/99)¹ require that stability testing for preservatives includes both the level of preservative and its efficacy:

The range of testing should cover not only chemical and biological stability but also loss of preservative, physical properties and characteristics, organoleptic properties, and where required microbiological attributes. Preservative efficacy testing and assays on stored samples should be carried out to determine the efficacy and content of antimicrobial preservatives.

and:

Any differences between the release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing.

These requirements are elaborated in three further Notes for Guidance adopted in Australia:

1. ***Note for Guidance on the Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products*** (CPMP/CVMP/QWP/115/95)²
2. ***Note for Guidance on Developmental Pharmaceutics*** (CPMP/QWP/155/96)³

These documents address the requirements for preservatives in liquid and semi-solid formulations that are not self-preserving. Preservative efficacy testing should be performed at the end of shelf-life and at the lower preservative limit in the end of shelf-life specification. Testing for content only is not sufficient because chemical concentration is not necessarily indicative of antimicrobial efficacy. In addition, for multi-dose containers, the efficacy must be established under simulated in-use conditions, to justify the proposed in-use shelf-life. If it is not logistically possible to conduct the complete in-use testing schedule in the original container, the use of an alternative container is acceptable provided that the product has been stored in the original container prior to the start of the in-use test.

¹ http://www.tga.gov.au/docs/html/euguide/euad_qual.htm#qualityactive

² http://www.tga.gov.au/docs/html/euguide/euad_qual.htm#qualitymedicinal

³ http://www.tga.gov.au/docs/html/euguide/euad_qual.htm#qualitygeneral

This testing could take the form of pharmacopoeial preservative efficacy testing with additional microbial challenges. Guidance may be obtained from the normative part of the international standard *ISO 14730: 2000 Ophthalmic Optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard dating*⁴⁵ which describes a test procedure and performance criteria for preservative efficacy over an open shelf life period of 28 days. The informative annexes include protocols where an open shelf-life of longer than 28 days is required. Where the open shelf-life is less than 28 days, the testing schedule should be adapted accordingly.

Alternatively, testing for microbial limits, preservative efficacy or sterility testing may be conducted on containers that have been used by patients or exposed to a pattern of use similar to that likely to be encountered during routine use.

3. *Note for Guidance on Maximum Shelf Life for Sterile Products After First Opening or Following Reconstitution (CPMP/QWP/159/96 Corr)*²

This document requires that information on how long sterile products may be used after opening should be included in the Product Information (PI). The information must be based on data generated in appropriate studies (described above), and recommendations.

⁴ <http://www.iso.ch/iso/en/ISOOnline.frontpage>

⁵ It should be noted that this reference is not being identified as a standard that must be applied to the product. It does, however, demonstrate the elements of the type of tests that may be applied to support an open shelf-life period.