The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 5 April 2000
CPMP/QWP/054/98 Corr

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

DECISION TREES FOR THE SELECTION OF STERILISATION METHODS (CPMP/QWP/054/98)

ANNEX TO NOTE FOR GUIDANCE ON DEVELOPMENT PHARMACEUTICS (CPMP/QWP/155/96)

DISCUSSION IN THE QUALITY WORKING PARTY	October 1997 January 1998
TRANSMISSION TO THE CPMP	January 1998
RELEASE FOR CONSULTATION	January 1998
DEADLINE FOR COMMENTS	July 1998
ADOPTION BY CPMP	February 1999
DATE FOR COMING INTO OPERATION	August 1999

Background:

These decision trees are intended to assist in the selection of the optimal sterilisation method and are proposed for inclusion as an annex to the Note for Guidance on Development Pharmaceutics. Reference is made to these Decision Trees in Section 5 (“Manufacturing Process”) of the Note for Guidance.

Minor modifications/corrections made in April 2000 to clarify titles of Decision trees and use of term product / formulation as appropriate.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (+44-20) 74 18 84 00 Fax: (+44-20) 74 18 85 51
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

DECISION TREES FOR THE SELECTION OF STERILISATION METHODS

(ANNEX TO NOTE FOR GUIDANCE ON DEVELOPMENT PHARMACEUTICS)

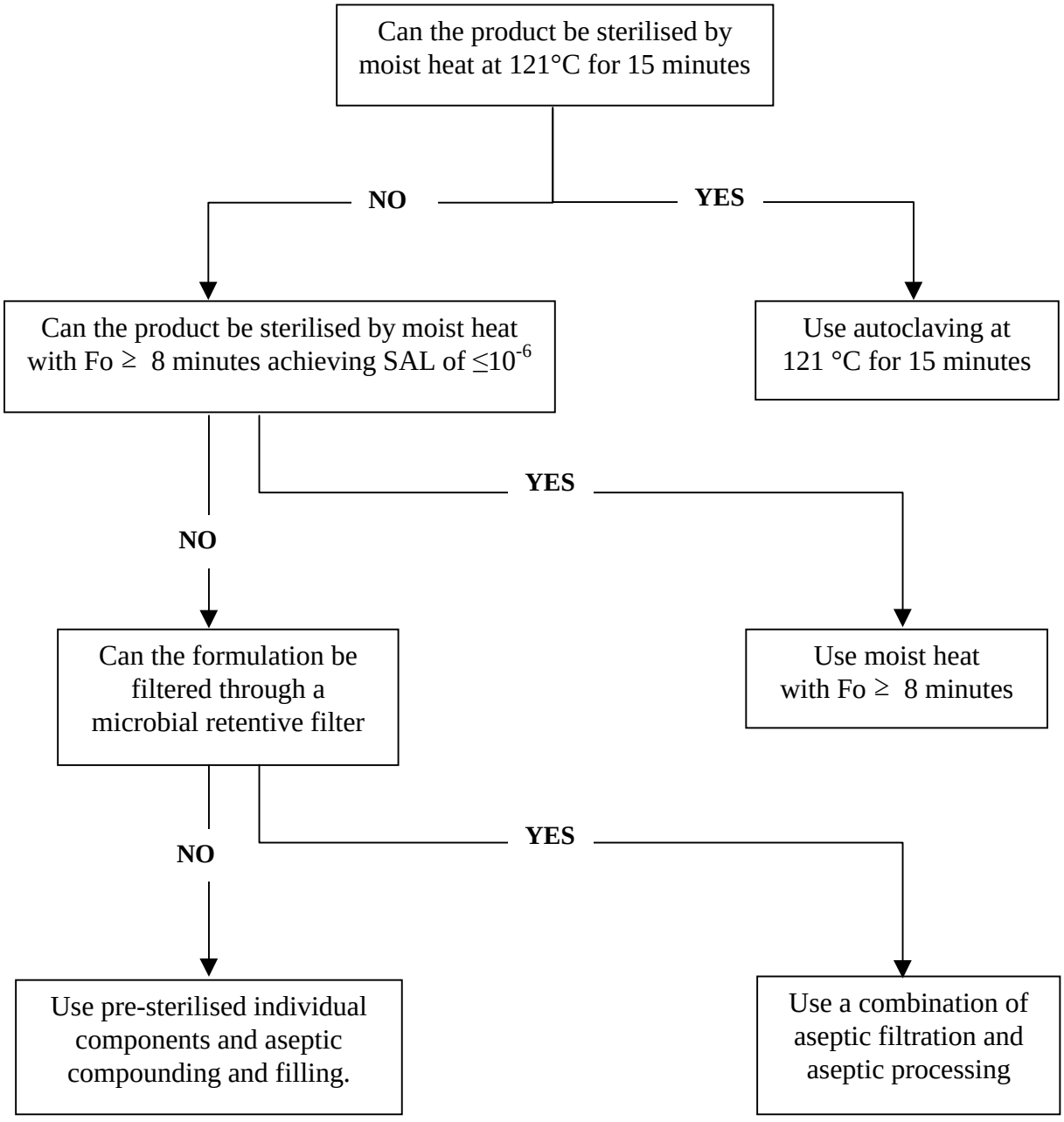
INTRODUCTION

Those products intended to be sterile should be terminally sterilised in their final container as clearly stated in the European Pharmacopoeia, and in the CPMP Notes for Guidance. Where it is not possible to carry out terminal sterilisation by heating due to formulation instability, a decision should be taken to utilise an alternative method of terminal sterilisation, filtration and/or aseptic processing. It is recognised that new terminal sterilisation processes other than those described in the pharmacopoeia may be developed to provide sterility assurance levels equivalent to present official methods, and such processes when properly validated may offer alternative approaches.

When moving down the decision trees it is clear that these methods generally show decreasing levels of sterility assurance, and it is therefore essential for product quality and safety to ensure that the highest level of sterility assurance is achieved in conjunction with the lowest level of pre-sterilisation bioburden appropriate. These decision trees are intended to assist in the selection of the optimal sterilisation method taking into account the various complicating factors. (A similar approach should be considered in the selection of sterilisation methods for intermediates to be incorporated into the finished product using aseptic processing).

The use of an inappropriate heat-labile packaging material cannot in itself be the sole reason for adoption of aseptic processing. Rather manufacturers should choose the best sterilisation method achievable for a given formulation and select the packaging material accordingly. However, it may be that the choice of a packaging material for a given product has to take into account factors other than the method of sterilisation. In such cases these other factors need to be clearly documented, explained and scientifically justified in the MA dossier. Conventionally, it has been accepted that other factors such as the type of container, route of administration and patient benefit have contributed to the choice of a particular container type, which will not withstand terminal heat sterilisation (e.g. certain ophthalmic products) and such products are therefore manufactured by validated aseptic processing. In such cases manufacturers have a duty to continue the search for acceptable alternative containers which would allow the move to the preferred terminal sterilisation in an acceptable timeframe. Commercial considerations should not be used as justification for not using terminal sterilisation with the highest possible level of sterility assurance.

DECISION TREE FOR STERILISATION CHOICES FOR AQUEOUS PRODUCTS



DECISION TREE FOR STERILISATION CHOICES
FOR NON-AQUEOUS LIQUID, SEMI-SOLID OR DRY POWDER PRODUCTS