REG-46 MAXIMUM SHELF-LIFE FOR STERILE PRODUCTS AFTER FIRST OPENING OR AFTER RECONSTITUTION

This provision is valid as of January 1, 2000

Introduction
In practice, there are frequently unclarities regarding the stability of sterile products after first opening or after reconstitution (dissolution or dilution). These unclarities concern requirements for submitted documentation, as well as the text of SPC, package leaflet and, where relevant, of labelling. As the European Union has already issued the Note for Guidance of the Committee for Proprietary Medicinal Products CPMP/QWP/159/96 „Maximum shelf-life for sterile products for human use after first opening or following reconstitution (issued on January 28, 1998, coming into operation in July 1998), which partly deals with this issue, its Czech translation is issued as a guideline of the State Institute for Drug Control.

It should be borne in mind that the stability of sterile products should be assessed both from the physico-chemical perspective and the microbiological perspective. For products which do not contain an antimicrobial additive and during whose preparation the risk of contamination was not eliminated, the only recommendation, from the microbiological point of view, is to use the product as soon as possible. This is, however, not always possible in practice, and storage times and conditions after opening and before use are the responsibility of the user. Results of chemical and physical stability submitted by the applicant in the registration process are provided for the user's information. For sterile products with antimicrobial preservative it is necessary to document storage time and conditions under which the product remains sterile after opening. It is equally important to note that information in this guideline relate to the time between opening the product and time of administration to the patient and are not an instruction for the physician on the product administration. For products where the process of administration itself can have an impact upon the stability of the product, the applicant should reflect this fact in the submitted documentation and information.

As a proof of shelf-life of sterile products after first opening or after reconstitution, the State Institute for Drug Control requires a stability study evidencing chemical and physical stability after opening or following reconstitution (in-use stability); for sterile products with antimicrobial preservative this study shall be accompanied by established efficacy of antimicrobial preservatives (ČL 97, 5.1.3.). The package leaflet, SPC, and possibly the labelling shall bear information the examples of which are, for various types of products, specified in the CPMP Note for Guidance (see italics).

CPMP/QWP/159/96
MAXIMUM SHELF-LIFE FOR STERILE PRODUCTS FOR HUMAN USE AFTER FIRST OPENING OR FOLLOWING RECONSTITUTION

GENERAL STATEMENT:
This guidance applies to all sterile products for human use, with the exception of Radiopharmaceuticals and extemporaneously prepared or modified preparations.
Because it is difficult to predict all the possible conditions, under which the product will be opened, diluted reconstituted and stored, etc., the user is responsible for maintaining the quality of the product that is administered to the patient. In order to help the user in this responsibility, the applicant should conduct appropriate studies and provide the relevant information in the User Information Texts, (e.g. SPC, Package insert, labels) following the examples given in italics bellow.
The applicant should also take note of the recommendations contained in the European Pharmacopoeia, with respect to storage times and conditions for specific categories of sterile products, once opened.
This guidance relates to the time between opening the product and time of administration to the patient; it takes no account of the duration of the administration process itself.

UNPRESERVED STERILE PRODUCTS
General
Chemical and physical in-use stability has been demonstrated for x hours/days at y ^{o}C.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Specific text for Preparations for Infusion or Injection
Chemical and physical, in-use stability has been demonstrated for x hours/days at y ^{o}C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ^{o}C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

AQUEOUS PRESERVED STERILE PRODUCTS (including antimicrobial preservatives or intrinsically self-preserving)
NON-AQUEOUS, E.G. OILY PREPARATIONS
Chemical and physical, in-use stability has been demonstrated for x hours/days at y ^{o}C.
From a microbiological point of view, once opened, the product may be stored for a maximum of z days at t ^{o}C.
Other in-use storage times and conditions are the responsibility of the user.

The applicant should justify the values of z and t on a case by case basis; z should not normally be greater than 28 days.