

STABILITY TESTING ON ACTIVE INGREDIENTS AND FINISHED PRODUCTS

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STABILITY TESTS ON ACTIVE INGREDIENTS AND FINISHED PRODUCTS

Note for guidance concerning the application of Part 2, section F of the Annex to Directive 75/318/EEC, as amended, with a view to the granting of a marketing authorisation for a new medicinal product.

1. INTRODUCTION

This note concerns research enabling the applicant to determine what shelf-life to propose.

The purpose of stability tests is to obtain information which enables proposals to be made for the shelf-life of the medicinal product and to recommend storage conditions.

The quality of a medicinal product is determined by its content of active substance(s), its purity (limitation or absence of decomposition products of the active substance(s)) and its organoleptic, physico-chemical and microbiological properties.

The purpose of the stability studies is to ascertain how the quality of a medicinal product varies as a function of time and under the influence of a variety of environmental factors.

On the basis of the information thus obtained, storage conditions are recommended (the purpose of these studies is to produce recommendations) which will guarantee maintenance of the quality of the medicinal product, in relation to its safety, efficacy and acceptability, throughout the proposed shelf-life (i.e. during storage, distribution, dispensing and use).

The design of the finished product stability studies for a medicinal product is based on the knowledge obtained from the studies on the active substance and from the Development Pharmaceutics studies.

2. INTRINSIC PROPERTIES OF THE ACTIVE INGREDIENT

Information on the stability of the active ingredient can be ascertained:

- for new active ingredient: by experimental studies;
- for known active ingredients: as a rule, evidence from the scientific literature is acceptable, but comparative accelerated stability studies may need to be considered in certain cases, such as when there is a significant change in the route of synthesis from that approved by the competent authorities, or when there is a significant change in the production method.

Where there are several possible active ingredient manufacturers and/or methods of obtaining the active ingredient, consideration may need to be given to the examination of studies on material from each source.

2.1 Batches examined

- the number of batches (minimum of two), together with the batch identification number, date of manufacture and size of each batch and the name of the manufacturer.

2.2 General methodology of the study

- details of the accelerated and proposed storage conditions used, taking into account the physical and chemical properties of the substance: temperature, humidity and light; exposure to air and chemical agents (particularly in solution in water and/or other solvents);
- duration of exposure under various conditions;
- materials and containers used.

2.3 Analytical methods

- the assay techniques used, normally with evidence from the analytical validation studies of their specificity (i.e. that they separate the active ingredient from its degradation products);
- method of determination (wherever possible) of the degradation products.

2.4 Results

- details of results obtained, as notes or numerical data, in table form.

2.5 Interpretation

- the conclusions as to the most appropriate storage conditions for the active ingredient, and the duration of storage before the substance needs retesting to check for compliance with specification;
- the discussion of the significance of the decomposition products, particularly as regards their potential toxicity.

2.6 Conclusions

The stability data on the active ingredient and the development studies enable a preliminary choice of the formulation and packing material to be made. They also enable some consideration to be given to the choice of analytical methods and test conditions for the studies on the pharmaceutical form.

3 STABILITY TESTS ON THE FINISHED PRODUCT

3.1 Objective

The analysis of the results of the stability studies on the finished product should allow the determination of the shelf-life, the recommendations for storage conditions (where relevant before and after opening the container), and the justification of any overage of the active ingredient applied to guarantee the potency at the end of the shelf-life.

The design of the stability tests is based on the known properties of the active ingredient (see section 2), the results of the Development Pharmaceuticals studies, the properties of the chosen formulation and the recommendations for use of the product.

The specifications proposed at the time of manufacture and to the end of the proposed shelf-life must reflect, as far as possible, the results of the stability studies, particularly in relation to any parameters which could have a bearing on efficacy and safety and product acceptability.

Specific in-use stability tests must be carried out where the product is labile once the container is opened, or where the product is to be diluted or reconstituted before use.

3.2 Study methods

3.2.1 Real-time studies

These studies should be carried out under a range of controlled test conditions which will enable the shelf-life and the product container label/package insert storage requirements to be defined. This will normally include studies which will allow the properties of the product at temperatures between 20°C and 30°C to be evaluated. However, 25°C should be used as the mean kinetic testing temperature for products in the European Union.

For each study, the mean temperature, the ranges of temperature and the mean humidity should be stated.

3.2.2 Studies under varied conditions

Such studies should be carried out to provide essential additional information. They can fulfil a number of objectives such as:

- to support the initial shelf-life request, by complementing the limited results of the early real-time studies as the decomposition, if it is occurring, is likely to be accelerated,
- to produce useful data at an early stage of development,
- to demonstrate the effects of adverse storage on the packaging and product, and to enable storage conditions and suitable labelling to be provided,
- to help to define suitable conditions for storage of the product,
- to support a request to extend the shelf-life,
- to support major changes in formulation, packaging materials or method of preparation.

The various test conditions should be stated. Depending on the nature and objectives of the stability study, the following may need to be considered:

- various test temperatures: three or more (see 3.7) particularly if long term real-time data is unavailable. The effect of low temperatures may, in addition, need to be considered such as below -15°C (freezer), 2-8°C (refrigerator) and freeze-thaw recycling,
- high humidity: relative humidity not less than 75%,
- elevated temperature and humidity in combination: e.g. temperature of 40°C associated with a relative humidity of 75%, possibly the effects of cycling between different temperatures and humidities,

- light: either natural day light or defined artificial illumination.

3.3 Definition of the product under study

3.3.1 Number and nature of the batches tested

The number of batches tested must be stated, with the batch number, details of the composition, date of manufacture, the size of the batch and the batch number and name of the manufacturer of the active ingredient(s) used. These should include where possible production scale batches of the product.

Normally at least 3 batches of the dosage form must be studied; however in circumstances where the active substance is an existing one (already used in licensed products), and it is found that the active substance is stable in the product and no significant decomposition products are formed, the stability study can be limited to 2 batches.

3.3.2 Immediate packaging

The batches of product must be packaged in the way proposed for marketing. However, supplementary evidence from batches of product in related packs must be used to augment this data.

Details of the packaging should be stated as:

- type(s) of container and closure, and nature of the constituent materials,
- nature of any desiccant used.

3.4 Characteristics

The characteristics studied should be:

- those in the finished product specification that are likely to be affected by storage, and
- those not monitored routinely at the time of manufacture, but which may be indicative of the stability/instability of the particular dosage form, e.g. dissolution of tablets.

3.4.1 Physical characteristics and microbiological aspects of the finished product

- organoleptic properties,
- physical properties specific to the dosage form, such as tablet hardness,
- important quality parameters such as the in vitro dissolution test, moisture content (e.g. in relation to any desiccant used in the packaging and particle size,
- efficacy of preservatives at the end of the reported storage test period or at the end of the shelf-life, except where otherwise justified,
- any other physical characteristics of the finished product that must be known in order to assess the product stability.

3.4.2 Chemical characteristics of the finished product

- assay of the active principle(s),
content of decomposition products,
- content of other agents (such as antimicrobial preservatives and antioxidants),
any other chemical characteristics that must be known in order to assess the quality of the product.

3.4.3 Characteristics of the packaging to be considered

- study of the container and closure interaction with the contents in any case where this is a risk.

3.5 Evaluation methods

The test methods used must be fully described. It must be shown that they are capable of detecting decomposition of the active ingredient in the medicinal product, and unless justified, of quantifying any decomposition products. If possible, the assay method for the active substance in the finished product should be stability indicating.

The test procedures applied to the stability tests on the finished product must be validated.

3.6 Presentation of results

The results should be summarised (e.g. as tables and graphs). For each batch of product, the initial results (at the time of manufacture), the results during storage and at the end of the proposed shelf-life should be given. However, results of real time data should be supplied as they become available.

3.7 Discussion, interpretation and conclusions

The discussion in the Expert Report should provide a critical evaluation of the suitability of the test methods used, the results obtained and proposed shelf-life specification.

If necessary to carry out any further studies due to significant changes in physical properties, an explanation should be given, together with the results of these studies.

Studies under accelerated test conditions will increase the decomposition and may permit some extrapolation of the room temperature shelf-life from that which would otherwise be acceptable. However, such studies would always need to be supplemented by long-term real time studies, and normally at least 6 month real time data should be presented in the application for marketing authorisation.

If batches of the product demonstrate a different stability profile, the shelf-life proposed and any average should be based on the stability of the least stable, unless an explanation can be given.

The shelf-life should be proposed for the product as packaged for sale. If necessary, a recommendation should also be given regarding the shelf-life before and after opening the container, and after dilution or reconstitution, and storage during marketing and use.

If there is evidence that batches of the stored product as packed for sale are stable at temperatures up to 30°C, the product need bear no special temperature storage instructions. However, if there is evidence that the product must be stored under defined conditions of storage, this must be stated on the container label and the package insert (if included). The maximum (or minimum) storage temperature should be stated in Celsius (e.g. store below 25°C, store in a refrigerator at 2-8°C, do not refrigerate – store above 8°C). These label/package insert storage recommendations must fully reflect conditions found in the Member State for which marketing authorisation is sought (see Annex), and those in any other Member State to which the product is likely to be supplied (whether by the person responsible for placing the product on the market or another person).

3.8 Ongoing stability

Where data on routine production batches is not provided in the application for marketing authorisation, ongoing stability studies should be carried out on 2 or 3 of the first production batches and the result provided to the competent authorities on an ongoing basis.

3.9 Variation to the marketing authorisation

Significant changes to the particulars and documents on which the marketing authorisation was approved, such as:

- major changes in composition,
- changes in packaging materials,
- major changes in the method of preparation for the product,

would normally necessitate the results of comparative accelerated or long term stability studies being provided to the competent authorities before such changes are introduced.

ANNEX

International Climatic Zones and Climatic Conditions

Climatic Condition	Zone I Temperate	Zone II Mediterranean (sub-tropical)	Zone III Hot/dry or Hot/moderate RH	Zone IV Very hot/humid
Mean Annual Temperature	< 20°C	20.5-24°C	>24°C	>24°C
Kinetic Mean Temperature (Virtual temperature)	21°C	26°C	31°C	31°C
Mean Annual Relative Humidity	45%	60%	40%	70%

Zones I and II are those in which EEC countries are situated.