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STABILITY TESTS ON ACTIVE SUBSTANCES AND FINISHED PRODUCTS : NEW EUROPEAN GUIDELINE.

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ABSTRACT

A new Note for Guidance on stability testing, data analysis, interpretation and labelling requirements for submission of information in Marketing Authorisation (MA) applications in the Member States of the European Community (EC) has recently been published. 25°C is recommended as the kinetic mean testing temperature for Real-time studies to allow products to be marketed in both Zone I (temperate climate) and Zone II (Mediterranean) European countries. Since climatic Zones I and II also include the USA, Canada and Japan, use of these storage test conditions would enable companies to generate data which could be used for marketing products in all of these territories.

INTRODUCTION

Harmonisation of national requirements for product quality in submissions for Marketing Authorisation (MA) in EC Member States is an essential prerequisite for the creation of a single European

market (of 325,000,000 consumers) in pharmaceutical products after 1992.

The complete 'Rules governing medicinal products in the European Community' was published in 1989 in 5 volumes. Volume I is the text of relevant Directives concerning medicinal products for human use[1]. Volume II is the information on procedures for national applications, Multi-state applications and concertation applications (for biotechnology and high technology products) and also the requirements for the MA dossier and the Expert Reports[2].

The Quality Working Party of the EC's Committee for Proprietary Medicinal Products (CPMP) considered all of the existing European national and other stability guidelines and produced the new version. This was adopted by the CPMP in 1988 after consultation with national authorities and considerable discussion and consultation with the European industry trade associations (EFPIA and AESGP). The new guideline is included in Volume III of the Rules[3]. The new guideline supersedes any earlier purely national guidelines on this subject. The guideline is meant to be read in conjunction with the general MA stability data requirements set out in Volume II of the Rules.

The function of a CPMP Note for Guidance is to provide a non-mandatory framework of information. They are a set of guidance notes from the EC authorities to the industry. They set out:

- the main points to be dealt with in the dossier for the marketing authorisation (MA) application;

- the minimum testing requirements (e.g. the number of batches of finished product to be tested);
- an indication in general terms of the methods, taking care not to go into technical details that are unnecessary to those skilled in the sciences of product, process and analytical development;
- examples of test requirements for specific products (e.g. to avoid frequently recurring problems in MA applications).

DEFINITIONS

The purpose of stability testing is to enable information to be generated (and provided to the authorities) which enables well-considered proposals to be made for the shelf-life of the medicinal product and the recommended storage conditions.

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

The quality of a medicinal product is determined by:

- its content of active substance,
- its purity (limitation or absence of degradation products of the active),
- its organoleptic properties,
- its physico-chemical properties,
- its microbiological properties.

The purpose of the label, leaflet and data-sheet storage recommendations isto guarantee the maintenance of the product quality in relation to its

safety and efficacy in use and its patient acceptability. The "label" recommendations need to include all aspects of storage, distribution, dispensing and use by the patient or his attendants.

CLIMATIC CONDITIONS AND RELATIONSHIP TO TEST CONDITIONS FOR LONG-TERM REAL-TIME TESTING

The reason for formal stability tests programmes is to carry out studies under defined conditions which simulate the adverse effects to which a medicinal product might be subjected during distribution, storage, handling and dispensing.

The world climate can be divided into four zones[4]:

Zone I : Temperate
Zone II : Mediterranean/sub-tropical
Zone III : Hot dry
Zone IV : Hot humid/tropical

Two fundamental factors which determine product stability during storage are Temperature and Relative Humidity. Haynes[5] derived a formula to calculate the kinetic mean temperature of storage (called the "virtual temperature" by Haynes) from individual temperatures over a period, taking into account the temperature dependency of the reaction rate by using the Arrhenius equation. This formula gives the possibility of expressing isothermal storage conditions to simulate the non-isothermal effects of variations in storage due to daily, seasonal and climatic variations in temperature and humidity.

In the EC, Northern European Countries (Belgium, Denmark, Federal Republic of Germany, Netherlands and Luxembourg) fall into Zone I. Southern European

TABLE 1. World Climatic Zones

Climatic Conditions	Zone I	Zone II	Zone III	Zone IV
Mean Annual Temperature	20.5°C	20.5-24°C	24°C	24°C
Kinetic Mean Temperature	21°C	26°C	31°C	31°C
Mean Annual Relative Humidity	45%	60%	40%	70%

countries (e.g. Greece, Portugal and Spain) fall into Zone II.

Products are often manufactured in one climatic Zone of the EC and then shipped to another for distribution, sale and patient use. Also, because of product price differentials in EC Member States, products are imported into high price countries from countries where product prices are lower (parallel importation). Some of this parallel importation is from Zone II countries (such as Greece and Spain) to Zone I (e.g. UK, Federal Republic of Germany and Netherlands).

For the future 'single European market', it is essential that labelling storage recommendations and shelf-life estimates reflect the worst conditions to which the product is likely to be subjected. Thus it

is no longer acceptable to store products under an undefined and uncontrolled so-called 'Room Temperature' in Northern Europe and then seek to apply this data to Zone II Southern Europe.

Using Haynes' method as developed by Grimm, other areas of the world can be assigned to their climatic zones. The USA is divided into Zone I (e.g. Chicago) and Zone II (e.g. Houston and Los Angeles). Japanese cities (Hiroshima, Osaka and Tokyo) fall overwhelmingly into Zone II. Thus, data generated under test conditions which simulate Zone II storage will provide data which should be suitable for all three of the major international pharmaceutical markets - the European Community, North America and Japan.

IMPLEMENTATION OF THE NEW EC STABILITY GUIDELINES

The text of the new guideline was adopted in 1988 and published formally in 1989. Its requirements should be implemented over 36 months after publication but any new stability studies started in the near future should be planned according to the new guideline.

DRUG SUBSTANCE STABILITY

For a New Active Substance (NAS), stability information will always be ascertained by experimental studies.

For existing, well-known active substances, (e.g. those in the pharmacopoeias) literature evidence cited in the MA application would normally be acceptable. However, comparative accelerated studies may be considered in certain circumstances (e.g. where there

is a significant change in the drug synthesis changing the impurity profile and potentially the stability). Studies may also be needed for ingredients of known problematic stability (e.g. coated ascorbic acid can discolour much more readily from some commercial sources).

Some of the active substance studies may be carried out as part of the Development Pharmaceutics Volume III of the Rules[3] includes a separate CPMP guideline on 'Development Pharmaceutics & Process Validation'.

Active substance stability studies include those designed to elucidate the conditions for degradation of the active, its potential route and degradation mechanism. Such studies involve exposing batches of the active to a variety of stress conditions - temperature, humidity, light, air and chemical agents (including buffers of varying pHs and solvents). The studies will enable likely degradation products to be identified and suitable stability - indicating analytical methods to be devised for specific assay of the active and quantitation of degradation products.

The studies on the active will indicate factors to be considered in formulating the product, in it's manufacture and the choice of pack.

The studies on the active enable definition of the required storage conditions and the retest date (e.g. the date at which conformity of batches of the drug substance to specification must be rechecked). The retest date is the equivalent for an active substance of the shelf-life.

The Note for Guidance indicates a minimum of 2 batches to be tested under a variety of temperature

and other conditions. The active substance must be assayed using a validated stability - specific method. It indicates that degradation products should be identified and quantitated using validated methods.

THE FINISHED PRODUCT

Batches of finished product must be tested according to a schedule of tests which include:

- evaluation of the shelf-life and consideration of label recommendations for storage conditions,
- evaluation of 'in use' stability date (particularly where the product is labile once opened or where it contains volatile ingredients, or could become contaminated),
- evaluation of 'in use' stability data where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection, an injection concentrate).

Stability trials will include both Real Time and Stress test studies (under a variety of conditions).

Real Time Studies

Real Time studies are a range of studies to enable the shelf-life and product packaging label/data-sheet storage recommendations to be defined. In the EEC this should now include studies at 25°C as the EEC kinetic mean temperature. The shelf-life will be defined from the product behaviour at 25°C but also taking into account the effects of exposure at temperatures up to 30°C for part of the year. At least 6 months' Real Time data need to be supplied in any application for a marketing authorisation.

Stress Tests

These provide complementary data to support the shelf-life request if long-term Real Time data is not available. They are also essential to determine what are the adverse effects on product and packaging of temperature (both high and low), humidity and light. These enable required label and data sheet storage conditions to be defined. The suggested test conditions include:

- 3 higher temperatures
- low temperatures (-15°C, 2-8°C and freeze-thaw cycling)
- high humidity (RH not less than 75%)
- high temperature and RH
- light (either natural day-light or artificial fluorescent light or Xenon lamp exposure)

It will clearly no longer be acceptable to merely only provide some minimal "Room Temperature" data without any stress test data and then label "store in a cool dry place" in complete ignorance of the possible real adverse effects of high temperature and humidity.

Low test temperatures are also important where products may be used in an emergency by a physician in the winter in Northern Europe. The product may freeze or precipitate and the user instructions should deal with the problem.

Number of Batches to be Tested

At least 3 batches must normally be studied but the guideline allows an exception where the active is known to be stable and also the product (including a

lack of degradation products) and no significant changes in other properties. If all of these criteria are satisfied, data on only 2 batches need be presented in the MA Application.

Although this is not stated explicitly in the guideline, for products with a number of different strengths of very closely related compositions (e.g. tablets where the main change is in compression weight), 'bracketing' of studies is acceptable; e.g. to study 3 batches of the highest and lowest strengths and a smaller number of intermediate strengths.

Immediate Packaging

The finished product in the studies must be packaged as proposed in the MA for marketing. However, supplementary data on batches stored in similar related packs may be used to augment this data.

Product Characteristics to be Studied

The guideline divides product characteristics into:

- physical characteristics (e.g. tablet hardness, particle size of suspension, in vitro dissolution),
- chemical characteristics (assay of active substance, content of degradation products),
- organoleptic properties,
- content of other agents,
- other chemical characteristics,
- microbiological characteristics (e.g. preservative efficacy at the end of the reported storage test or at the end of the shelf-life)

- packaging characteristics (study of any product/container interaction).

The characteristics which need to be studied should be:

- those in the finished product specification which are likely to be affected by storage,
- those not monitored in the finished product specification which may be indicative of stability.

The EC guideline, in contradistinction to the FDA Guideline[7], does not recommend parameters that need to be monitored for specific products (e.g. tablets, capsules, emulsions, oral solutions, powders, aerosols, topical and ophthalmic preparations, small and large volume parenterals etc). The FDA list of products is not exhaustive and it was felt better to indicate the general principles of the testing and to leave the detailed consideration for the manufacturer to judge and justify in the light of his more detailed knowledge of the specific product.

Test Method Validation

All stability test methods must be validated and the method validation data included in the MA application.

Data Presentation

Tables and graphs are preferred.

Discussion and Analysis of Data

A detailed discussion and analysis of the data must now be provided in the Pharmaceutical expert

Report[2]. The evaluation of the data should be statistical where possible[7].

Some points to be borne in mind in the data analysis may include:

- the concept of 'material balance' (the idea of reviewing the assays and levels of degradation products together to see if the observed degradation products account for all of the degradation).
- the least stable batch. If product batches have a significantly different stability, the shelf-life and overage must be based on the least stable batch (unless an explanation can be provided for the difference). - shelf-life after opening - a separate label/pack insert/data sheet warning may be needed of the shelf-life after first opening
- shelf-life after reconstitution and/or dilution. Details of all diluents need to be explicitly provided and data given on both physical stability and the assay to support the recommendations.

Labelling

The aim is to have a single set of label recommendations for the EC and to allow products to be moved freely within the market. The guideline recommends that:

- if there is evidence that defined storage conditions are needed, these must be stated specifically on the label in °C (e.g. store below 25°C, store in a refrigerator at 2-8°C, etc)

- if the product is stable at 30°C, the product need bear no special temperature storage instructions.

Ongoing Stability

If data on production-scale batches are not provided, ongoing studies should be carried out on the first 2 or 3 production batches and the results provided to the authorities on a regular basis.

Variations

Any significant changes to the particulars and documents (e.g. change in immediate packaging) would normally need the results of comparative, accelerated, or long-term Real Time stability studies to be provided.

Need for New Labelling of Existing Products.

Labelling of existing licensed products to use defined storage test conditions in °C should be brought in for existing products at the renewal of their 5-year marketing authorisations. Companies should review the existing stability data and justify the new label recommendations.

CONCLUSIONS

Well designed stability studies according to this guideline could be carried out to meet the requirements for an International core registration dossier for Manufacturing & Controls. The new stability requirements might, with some adaptation, also meet Japanese requirements[a] and, in the future, it is hoped that the Japanese authorities might

recognise data generated according to EC protocols, since it is designed to cover Zone II countries such as Japan.

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