

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96D-0010]

International Conference on Harmonisation; Guideline for the Photostability Testing of New Drug Substances and Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guideline entitled "Guideline for the Photostability Testing of New Drug Substances and Products." The guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline describes the basic testing protocol for photostability testing of new drug substances and products in original new drug application submissions. The guideline is an annex to the ICH guideline entitled "Stability Testing of New Drug Substances and Products."

DATES: Effective May 16, 1997. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Copies of the guideline are available from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Nancy B. Sager, Center for Drug Evaluation and Research (HFD-357), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5721.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically

based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the **Federal Register** of March 7, 1996 (61 FR 9310), FDA published a draft tripartite guideline entitled "Guideline for the Photostability Testing of New Drug Substances and Products." The notice gave interested persons an opportunity to submit comments by June 5, 1996.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held on November 5, 1996.

In the **Federal Register** of September 22, 1994 (59 FR 48754), the agency published a guideline entitled "Stability Testing of New Drug Substances and Products." The guideline addresses the generation of stability information for submission to FDA in new drug applications for new molecular entities and associated drug products. In the discussion of "stress testing" for both drug substances and drug products, the guideline states that "light testing" should be an integral part of stress

testing and will be considered in a separate ICH document.

This guideline is an annex to that guideline and describes the basic testing protocol for photostability testing of new drug substances and products in original new drug application submissions.

This guideline represents the agency's current thinking on photostability testing of new drug substances and products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guideline is available on the Internet using the World Wide Web (WWW) (<http://www.fda.gov/cder/guidance.htm>).

The text of the guideline follows:

Guideline for the Photostability Testing of New Drug Substances and Products

I. General

The ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline) notes that light testing should be an integral part of stress testing. This document is an annex to the parent guideline and addresses the recommendations for photostability testing.

A. Preamble

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described under "Selection of Batches" in the parent guideline. Under some circumstances these studies should be repeated if certain variations and changes are made to the

product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation and/or change made.

The guideline primarily addresses the generation of photostability information for submission in registration applications for new molecular entities and associated drug products. The guideline does not cover the photostability of drugs after administration (i.e., under conditions of use) and those applications not covered by the parent guideline. Alternative approaches may be

used if they are scientifically sound and justification is provided.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:

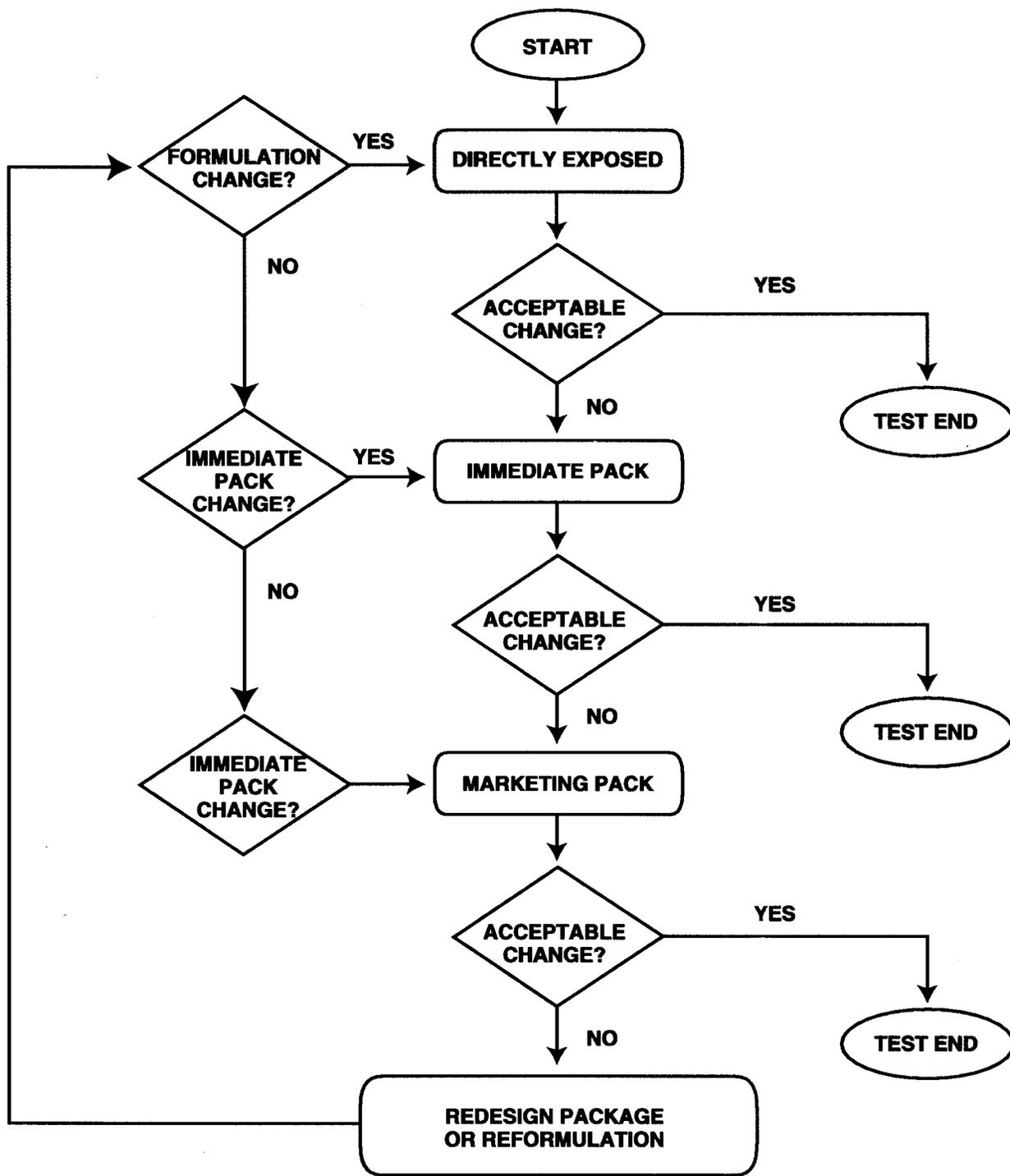
- (i) Tests on the drug substance;
- (ii) Tests on the exposed drug product outside of the immediate pack; and if necessary;
- (iii) Tests on the drug product in the immediate pack; and if necessary;
- (iv) Tests on the drug product in the marketing pack.

The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing as described in the Decision Flow Chart for Photostability Testing of Drug Products. Acceptable change is change within limits justified by the applicant.

The formal labeling requirements for photolabile drug substances and drug products are established by national/regional requirements.

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DECISION FLOW CHART FOR PHOTOSTABILITY TESTING OF DRUG PRODUCTS



B. Light Sources

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. For both options 1 and 2, a pharmaceutical manufacturer/applicant may rely on the spectral distribution specification of the light source manufacturer.

Option 1

Any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nanometers (nm), an appropriate filter(s) may be fitted to eliminate such radiation.

Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp.

1. A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977 (1993); and

2. A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

C. Procedure

For confirmatory studies, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter to allow direct comparisons to be made between the drug substance and drug product.

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure is provided in the Annex.

If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample.

II. Drug Substance

For drug substances, photostability testing should consist of two parts: Forced degradation testing and confirmatory testing.

The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the

analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. For development and validation purposes, it is appropriate to limit exposure and end the studies if extensive decomposition occurs. For photostable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified.

Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be examined further.

Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling (see section I.C., Procedure, and I.I.A., Presentation of Samples, for information on the design of these studies).

Normally, only one batch of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guideline if the drug is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. Samples should be selected as described in the parent guideline.

A. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts should be made, such as cooling and/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation, or melting are minimized. All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

As a direct challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary. Solid drug substances should be spread across the container to give a thickness of typically not more than 3 millimeters. Drug substances that are liquids should be exposed in chemically inert and transparent containers.

B. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance,

clarity or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations, such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark control if these are used in the test.

C. Judgment of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product, and if light resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies in order to assure that the drug will be within justified limits at time of use (see the relevant ICH Stability and Impurity Guidelines).

III. Drug Product

Normally, the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light. The drug product should be exposed to the light conditions described under the procedure in section I.C.

Normally, only one batch of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guideline if the product is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted on directly exposed drug product.

It may be appropriate to test certain products, such as infusion liquids or dermal creams, to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

A. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts, such as cooling and/or placing the samples in sealed containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting. All such precautions should be chosen to provide minimal interference with the irradiation of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

Where practicable when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance. The samples should be positioned to provide maximum area of exposure to the light source. For example, tablets, capsules, should be spread in a single layer.

If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz).

If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large volume containers (e.g., dispensing packs).

B. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution, dissolution/disintegration for dosage forms such as capsules) and for assay and degradants by a

method suitably validated for products likely to arise from photochemical degradation processes.

When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions). The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

C. Judgment of Results

Depending on the extent of change, special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order to assure that the product will be within proposed specifications during the shelf life (see the relevant ICH Stability and Impurity Guidelines).

IV. Annex

A. Quinine Chemical Actinometry

The following provides details of an actinometric procedure for monitoring exposure to a near UV fluorescent lamp (based on FDA/National Institute of Standards and Technology study). For other light sources/actinometric systems, the same approach may be used, but each actinometric system should be calibrated for the light source used.

Prepare a sufficient quantity of a 2 percent weight/volume aqueous solution of quinine monohydrochloride dihydrate (if necessary, dissolve by heating).

Option 1

Put 10 milliliters (mL) of the solution into a 20 mL colorless ampoule, seal it hermetically, and use this as the sample. Separately, put 10 mL of the solution into a 20 mL colorless ampoule (see note 1), seal it hermetically, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure determine the absorbances of the sample (A_T) and the control (A_O) at 400 nm using a 1 centimeter (cm) pathlength. Calculate the change in absorbance, $\Delta A = A_T - A_O$. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.9.

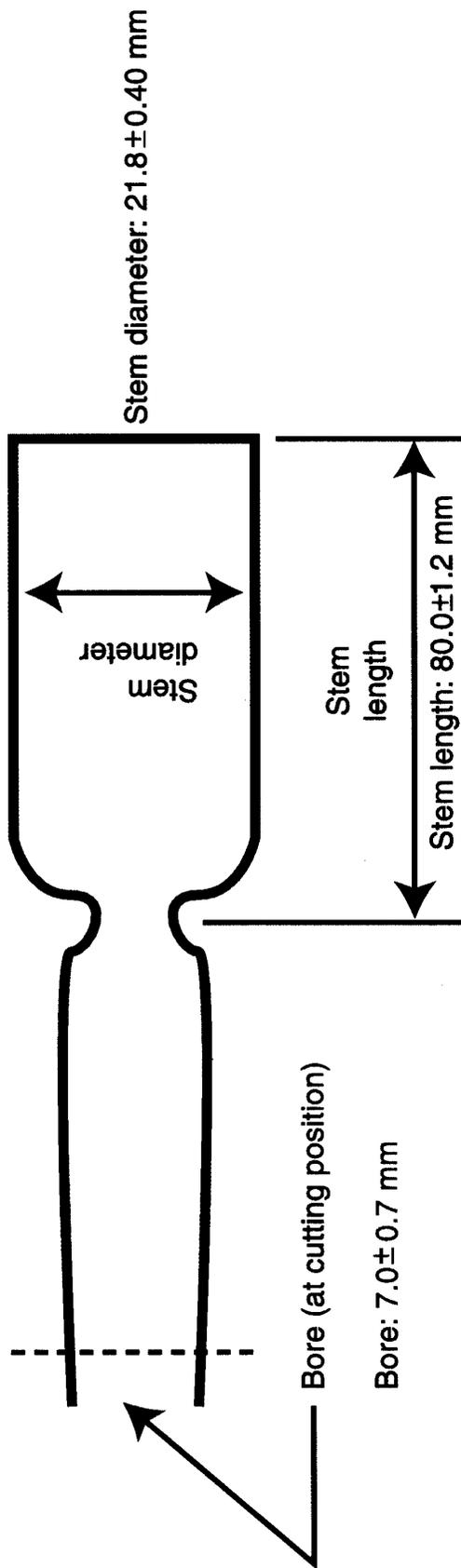
Option 2

Fill a 1 cm quartz cell and use this as the sample. Separately fill a 1 cm quartz cell, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure determine the absorbances of the sample (A_T) and the control (A_O) at 400 nm. Calculate the change in absorbance, $\Delta A = A_T - A_O$. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.5.

Alternative packaging configurations may be used if appropriately validated. Alternative validated chemical actinometers may be used.

Note 1: Shape and Dimensions (See Japanese Industry Standard (JIS) R3512 (1974) for ampoule specifications)

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V. Glossary

- Immediate (primary) pack is that constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

- Marketing pack is the combination of immediate pack and other secondary packaging such as a carton.

- Forced degradation testing studies are those undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the

material for method development purposes and/or degradation pathway elucidation.

- Confirmatory studies are those undertaken to establish photostability characteristics under standardized conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light-resistant packaging and/or special labeling is needed to mitigate exposure to light. For the confirmatory studies, the batch(es) should be selected according to batch selection for long-term and accelerated testing which is described in the parent guideline.

VI. References

Yoshioka, S., et al., "Quinine Actinometry as a Method for Calibrating Ultraviolet Radiation Intensity in Light-Stability Testing of Pharmaceuticals," *Drug Development and Industrial Pharmacy*, 20(13):2049-2062, 1994.

Dated: May 2, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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