DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96D–0010]

International Conference on Harmonisation; Draft 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 draft guideline entitled ''Guideline for the Photostability Testing of New Drug Substances and Products.'' The draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline describes the basic testing protocol for photostability testing of new drug substances and products in original new drug application (NDA) submissions. The draft guideline is an annex to the ICH guideline entitled ''Stability Testing of New Drug Substances and Products.''

DATES: Written comments by June 5, 1996.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft guideline are available from the Division of Communications Management (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1012. An electronic version of this draft guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Robert J. Wolters, Center for Drug Evaluation and Research (HFD–110), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5300.

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.

At a meeting held on November 29, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Guideline for the Photostability Testing of New Drug Substances and Products'' should be made available for public comment. The draft guideline is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Quality Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's guideline.

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 NDA's 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 draft guideline is an annex to that guideline and describes the basic testing protocol for photostability testing of new drug substances and products in original NDA submissions.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Although this guideline does not create or confer any rights on or for any person and does not operate to bind FDA in any way, it does represent the agency's current thinking on photostability testing of new drug substances and products.

Interested persons may, on or before June 5, 1996, submit written comments on the draft 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 draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Guideline for the Photostability Testing of New Drug Substances and Products

I. General

The ICH Harmonized Tripartite Guideline covering the 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 are repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation and/or change made, but photostability testing is not part of stability studies for marketed products.

The guideline seeks to describe the basic testing protocol for photostability testing of

new drug substances and products at the time of the first submission. Alternative approaches are acceptable 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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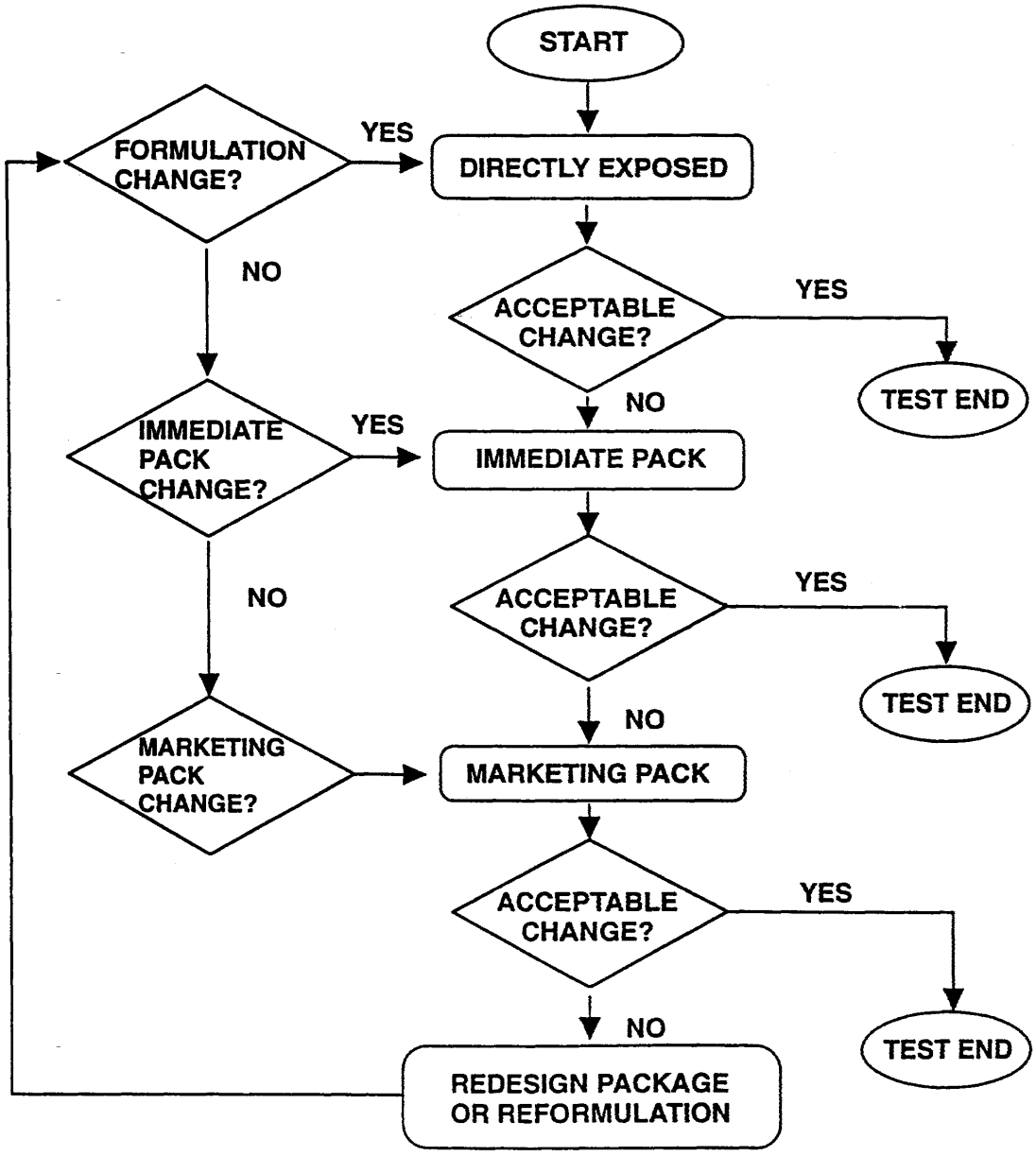
DECISION FLOW CHART FOR PHOTOSTABILITY TESTING OF DRUG PRODUCTS



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B. Light Sources

The light sources described below may be used for photostability testing. To minimize the effect of localized temperature changes, the applicant should either maintain an appropriate control of temperature 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), a window glass filter may be fitted to eliminate such radiation.

Option 2

1. A cool white fluorescent lamp as defined 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 (e.g., quinine for near UV region) 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.

Any protected samples (e.g., wrapped in aluminum foil) used as dark controls 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 II.A., Presentation, 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 fully exposed product then progressing as necessary to product in the immediate pack and 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 the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, which are intended for direct dispensing to the patient, testing should normally only be conducted on directly exposed drug product.

It may be appropriate to test certain products such as infusion liquids, and 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 and 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 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) 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 necessary 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 the primary actinometric procedure for monitoring exposure to the near UV region of the light source. The actinometric systems should be calibrated for the type of sources used.

Prepare a sufficient quantity of a 2 percent weight/volume aqueous solution of quinine monohydrochloride dihydrate (if necessary dissolve by heating). 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) pathway. Calculate the change in absorbance, $\Delta A = A_T - A_O$.

For near UV lamps, the length of the exposure should be sufficient to ensure a change in absorbance observed of at least 0.8.

Alternative packaging configurations (e.g., use of a 1 cm fused silica cell) may be used if appropriately validated. Alternative validated chemical actinometers may be used.

Note 1: Shape and Dimensions

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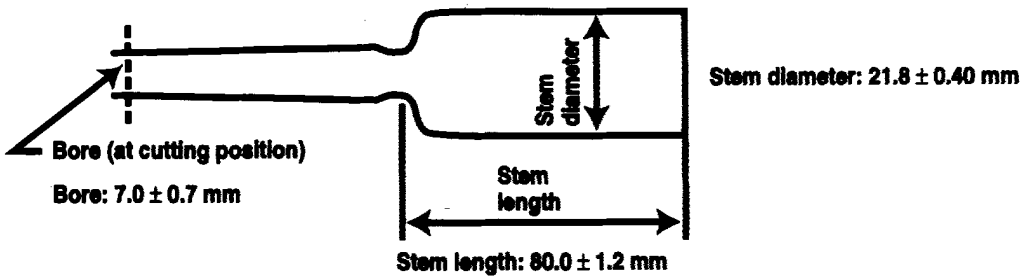

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V. Glossary

- 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 substance, 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.

VI. Reference

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: February 27, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–5295 Filed 3–6–96; 8:45 am]

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