USP 24
NF 19

U.S. Pharmacopeia & National Formulary

2000

USP 24

THE UNITED STATES PHARMACOPEIA

NF 19

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 9–12, 1995. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 2000

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

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ISSN 0195-7996
ISBN 1-889788-03-1

Printed by National Publishing, Philadelphia, PA

CALIBRATION

For purposes of calibration, one of the following reference materials may be used, as required by instrument geometry. For transmittance measurements, purified water may be used as a white standard and assigned a transmittance of 1.000 at all wavelengths. Then the tristimulus values X, Y, and Z for CIE source C are 98.0, 100.0, and 118.1, respectively. For reflectance measurements, opaque porcelain plaques, whose calibration base is the perfect diffuse reflector and whose reflectance characteristics have been determined for the appropriate instrumental geometry, may be used.[2] If the geometry of sample presentation precludes the use of such plaques, pressed barium sulfate, white reflectance standard grade, may be used.[3]

After calibration with the above-mentioned materials, it is desirable whenever possible to measure a reference material as close to the color of the sample as possible. If a sample of the material being tested is not suitable for use as a long-term standard, color chips are available[4] which span the entire visually uniform color space in small increments. The use of such a reference standard is encouraged as a means of monitoring instrument performance even for absolute color determinations.

SPECTROPHOTOMETRIC METHOD

Determine the reflectance or transmittance from 380 to 770 nm at intervals of 10 nm. Express the result as a percentage, the maximum being 100.0. Calculate the tristimulus values X, Y, and Z as follows.

Reflecting Materials—For reflecting materials the quantities X, Y, and Z are

$$X = \sum_{380}^{770} \rho_\lambda \bar{x}_\lambda P_\lambda \Delta\lambda / Y',$$

$$Y = \sum_{380}^{770} \rho_\lambda \bar{y}_\lambda P_\lambda \Delta\lambda / Y', \text{ and}$$

$$Z = \sum_{380}^{770} \rho_\lambda \bar{z}_\lambda P_\lambda \Delta\lambda / Y',$$

in which $Y' = \sum_{380}^{770} \bar{y}_\lambda P_\lambda \Delta\lambda$, ρ_λ is the spectral reflectance of the material, $\bar{x}_\lambda P_\lambda$, $\bar{y}_\lambda P_\lambda$ and $\bar{z}_\lambda P_\lambda$ are known values associated with each Standard Source,[1,2] and $\Delta\lambda$ is expressed in nm.

Transmitting Materials—For transmitting materials, the quantities X, Y, and Z are calculated as above, τ_λ (spectral transmittance) being substituted for ρ_λ.

COLORIMETRIC METHOD

Operate a suitable colorimeter[5] to obtain values equivalent to the tristimulus values, X, Y, and Z. The accuracy with which the results obtained from the filter colorimeter match the tristimulus values may be indicated by determining the tristimulus values of plaques of strongly saturated colors and comparing these values with those computed from spectral measurements on a spectrophotometer.

Interpretation

COLOR COORDINATES

The Color Coordinates, L^*, a^*, and b^* are defined by

$$L^* = 116\ (Y/Y_o)^{1/3} - 16,$$
$$a^* = 500\ [(X/X_o)^{1/3} - (Y/Y_o)^{1/3}], \text{ and}$$
$$b^* = 200\ [(Y/Y_o)^{1/3} - (Z/Z_o)^{1/3}],$$

in which X_o, Y_o, and Z_o are the tristimulus values of the nominally white or colorless standard, and $Y/Y_o > 0.01$. Usually they are equal to the tristimulus values of the standard illuminant, with Y_o set equal to 100.0. In this case $X_o = 98.0$ and $Z_o = 118.1$.

COLOR DIFFERENCE

The total Color Difference ΔE^* is

$$\Delta E^* = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2},$$

in which ΔL^*, Δa^*, and Δb^* are the differences in color coordinates of the specimens being compared.

Instrumental variables can influence results. Although reliable comparisons can be made between similar colors measured concomitantly, results obtained on different instruments or under different operating conditions should be compared with caution. If it is necessary to compare data obtained from different instruments or taken at different times, etc., it is very helpful to have concomitant data obtained on a standard reference material such as color chips for opaque materials. Comparison of the readings on the reference material helps to identify variations caused by instrument performance.

[2] Suitable items are available from BYK-Gardner USA, 2431 Linden Lane, Silver Spring, MD 20910, or from Hunter Associates Laboratory, Inc., 11491 Sunset Hills Road, Reston, VA 22090.

[3] Suitable material is available from Eastman Kodak Company, Rochester, NY 14650, as "White Reflectance Standard."

[4] Centroid Color Charts may be obtained from suppliers of instruments for measurement of color.

[5] A suitable tristimulus colorimeter is available from BYK-Gard-

⟨1074⟩ EXCIPIENT BIOLOGICAL SAFETY EVALUATION GUIDELINES

INTRODUCTION

This informational chapter presents a scientifically-based approach for the safety assessment of new pharmaceutical excipients (i.e., those excipients that have not been previously used or permitted for use in a pharmaceutical preparation). The guidelines presented herein provide a protocol for developing an adequate database upon which to establish conditions for the safe use of a new excipient intended for use in products administered by various dosage routes. [NOTE—The final section of this chapter, *Definition of Terms*, lists some terms referred to in this chapter.]

An excipient may perform a variety of functionality roles in a pharmaceutical product; but, unlike pharmacologically active drug entities, the excipient displays either no pharmacological activity or very limited and directed activity. Because of these differences between excipients and active drug substances in terms of risk and benefit relationships and expected biological activities, the approaches for safety assessments of excipients and active drug substances will differ. Therefore, it is important to note that the guidelines presented in this informational chapter apply only to the safety assessment of excipients, not to the safety assessment of active drug substances.

These testing guidelines are informational in nature and are intended to be used by professionals having a knowledge of toxicology and associated sciences. It is also intended that the applicable safety test method requirements of the receiving regulatory authority would be used in a proposal for market entry. For example, if a proposal is to be submitted to the U.S. Food and Drug Administration, that agency's safety test requirements would have to be met. These guidelines do not provide specific details regarding test methodology and data interpretation. Test procedures that are generally recognized by experts and by the regulatory agencies should be used. Alternatives to the use of living animals are encouraged wherever these alternative procedures have been validated for the intended purpose and where it is known that the alternative procedure will provide sufficient data upon which to base a safety judgment. It is recommended that the *Guiding Principles on the Use of Animals in Toxicology* of the Society of Toxicology (1996) and, in other countries, the appropriate legal and professional codes, be adhered to in the conduct of all test procedures. All studies must meet the requirements of the appropriate national good laboratory practice guidelines in effect in the country where the studies are

guidelines for orally-ingested excipients only. In addition, there may be animal-based data, which was developed for other purposes, that may be used to fulfill the testing guidelines requirements. If the data requirements have been met through prior human use experience and pertinent human data have been collected in a scientifically sound manner, there is no need to provide animal data for those endpoints evaluated by prior clinical experience.

Some dosage routes offer unique toxicological challenges, and the guidelines include provisions for these routes (e.g., inhalation). Also, further explanation is provided regarding numbers of species and other basic information (e.g., two species, one rodent and one nonrodent).

The extent of information required to define a set of baseline data, which constitute a toxicological and chemical database, is dependent upon the intended use of, and duration of, dosing of the candidate excipient material. It is critical that a thorough review of background information be conducted before embarking on a testing regimen. In addition to literature database reviews, information should be obtained regarding the physical and chemical properties of the compound; its manufacturing process (or processes); and product specifications including limits of impurities, potential for pharmacological activity, exposure conditions (i.e., dose, duration, frequency of use, dosage formulation, and route of administration), and potential user population. Also, base toxicity information covering the topics is fundamental. Particular attention should be addressed to the absorption/distribution/metabolism/excretion/pharmacokinetics (ADME/PK) studies because much of the later decision process will be dependent upon these data.

These guidelines provide a mechanism for obtaining sets of baseline data for all candidate excipient materials. The background information and baseline toxicity information alone may support the use of the candidate excipient either in a short half-life product that is not administered in a frequency that results in a residual excipient build-up in body tissue or in a product used only once or twice in a lifetime, such as a diagnostic agent. Additional tests, listed under Step 4 of the *Safety Assessment Guidelines*, are necessary for candidate excipient material that is to be used in a manner that will result in short- or intermediate-term repeated exposure in humans—that is, a pharmaceutical product that will be administered for less than 10 days or for 30 to 90 consecutive days, respectively. For a candidate excipient material that is intended for use in a pharmaceutical product intended for either intermittent or chronic administration over a long time period, such as a treatment for psoriasis or an insulin preparation, further tests are required. These tests are listed under Step 7 of the guidelines and in the appropriate section under *Additional Requirements for Specific Exposure Routes*. While providing guidance for consumer safety, some of the required tests are intended to provide information to address occupational safety (e.g., skin and eye irritation).

The guidelines are summarized in Table 1. Tests that are required (R) by the guidelines are distinct from those that are recommended conditionally (C). Whether conditional tests are conducted is dependent upon the conditions of use and available biological data. Consideration must also be given to the requirements of the regulatory authorities when making the decision to test.

Table 1. Summary of Excipient Guidelines.

Tests	Routes of Exposure for Humans					
	Oral	Mucosal	Dermal/Topical/ Transdermal	Injectable*	Inhalation/ Intranasal	Ocular
Baseline Toxicity Data						
Acute Oral Toxicity	R	R	R	R	R	R
Acute Dermal Toxicity	R	R	R	R	R	R
Acute Inhalation Toxicity	C	C	C	C	R	C
Eye Irritation	R	R	R	R	R	R
Skin Irritation	R	R	R	R	R	R
Skin Sensitization	R	R	R	R	R	R
Acute Injectable Toxicity	—	—	—	R	—	—
Application Site Evaluation	—	—	R	R	—	—
Pulmonary Sensitization	—	—	—	—	C	—
Phototoxicity/Photoallergy	R	—	R	R	R	—
Genotoxicity Assays	R	R	R	R	R	R
ADME/PK-Intended Route	R	R	R	R	R	R
28-Day Toxicity (2 Species)-Intended Route	R	R	R	R	R	R
Additional Data: Short- or Intermediate-term Repeated Use						
90-Day Toxicity (Most Appropriate Species)	R	R	R	R	R	R
Embryo-Fetal Toxicol.	R	R	R	R	R	R
Additional Assays	C	C	C	C	C	C
Genotoxicity Assays	R	R	R	R	R	R
Immunosupression Assays	R	C	C	R	C	C
Additional Data: Intermittent Long-term or Chronic Use						
Chronic Toxicity (Rodent, Nonrodent)	C	C	C	C	C	—
Reproductive Toxicity	R	R	R	R	C	C
Photocarcinogenicity	C	—	C	C	R	R
Carcinogenicity	C	C	C	C	C	—

R = Required

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