BASIC TESTS FOR PHARMACEUTICAL SUBSTANCES

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CONTENTS

The tests described in this manual are intended only to verify the identity of pharmaceutical substances and to detect or exclude gross degradation. They should not be used to replace the monographs contained in the *International Pharmacopoeia*. As a first step, tests have been devised for the majority of drug substances contained in the WHO Model List of Essential Drugs as well as for a number of other widely used drug substances. Analogous tests for substances in dosage forms are in preparation.

1. INTRODUCTION

The simplified tests (basic tests) for drug substances described in this manual represent one element of quality assurance in the pharmaceutical supply system.

They have been devised with the following objectives:

(*a*) to provide a simple and readily applicable method for verifying the identity of a drug substance, using a limited range of widely available reagents, when the labelling and physical attributes of the substance do not provide adequate confirmation;

(*b*) to provide a practicable means for confirming the identity of a drug, when a fully equipped laboratory is not available;

(*c*) to indicate if gross degradation has occurred in certain substances that are known to decompose readily under adverse conditions.

Basic tests are not, in any circumstances, intended to replace the requirements of pharmacopoeial monographs. The latter give an assurance of quality whereas basic tests merely confirm identity.

In several European countries, simple tests have already been endorsed by the national pharmaceutical associations for use at peripheral levels of distribution (wholesale premises, pharmacies) to verify the identity of pharmaceutical substances whenever the possibility of confusion arises and sometimes to exclude gross degradation or adulteration.

Degradation during storage and transportation is of particular importance in tropical countries. Indeed, an expiry date determined for a temperate climate may be inappropriate in a tropical region even when adequate containers are used. For this reason, the stability characteristics of most of the substances referred to in this manual have been determined and tests to indicate gross degradation are presented for the least stable substances.

Basic tests need not be carried out by fully qualified pharmacists or chemists, but they should be performed by persons who have some understanding of analytical chemistry such as that acquired in courses for pharmaceutical assistants.

Several tests are described for most substances. Not all of these need to be applied to any one sample. One test concerned with melting

behaviour, together with two test-tube reactions, will suffice in most circumstances. If, however, there is any reason to suspect that the product is mislabelled or substandard, all tests described should be performed. By their nature, simplified tests cannot be completely reliable. An adverse result, even in one test, should be taken as a warning of potential unsuitability of a drug. In these circumstances, a final conclusion should not be drawn until a full analytical examination has been carried out in a properly equipped analytical laboratory.

The reagents and equipment required for these tests have been kept to a minimum. Reagents that are unstable, corrosive, expensive or difficult to obtain have been excluded.

The use of visual or similar characteristics for initial assessment is self-evident. Attributes such as colour and characteristic odour of the sample should always be noted.

Some of the individual tests, such as those referring to a change in the physical aspect of the test substance, call for comparison against a standard. Each laboratory where basic tests are routinely performed should therefore retain a collection of authentic samples of frequently analysed substances. Such a collection may be established from small amounts of substances previously tested and found to be satisfactory. These provide a standard of comparison both for visual characteristics and test-tube reactions.

In general, the following types of test have been preferred:

—classical chemical techniques such as colour reactions, the formation of precipitates with specific reagents, the evolution of gas and its identification, and the behaviour of substances on heating. In some instances these reactions lack specificity since drugs with similar functional groups may not be distinguishable by simple chemical reactions;

—the appearance of a concentrated solution of a substance in selected solvents. This can be useful for detecting degradation products and the presence of some other impurities.

The techniques used to determine melting characteristics are described in particular detail. They provide a basis not only for confirming the identity of a substance but also for detecting possible contamination, whether arising from poor manufacture, adulteration, cross-contamination during storage, or degradation.

The capillary method has been selected for use in basic tests. Other techniques, such as the microscopic hot bench or melting block, are applicable, but the results of different methods are not directly comparable.

It should be noted that the terms used to describe the melting characteristics are different from those adopted in the *International Pharmacopoeia*, since pharmacopoeial specifications are based on more rigorous methods.

Basic tests for finished pharmaceutical forms are planned to follow this publication.

Comments on the tests described are invited and should be addressed to:

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2. DETERMINATION OF MELTING CHARACTERISTICS

2.1 Determination of melting point

2.1.1 *Definition*

The melting point is determined in a capillary tube. The expression "melts about . . . " means that the temperature at which the substance is completely melted, as indicated by the disappearance of the solid, will be in the range ±4 °C from the stated value, unless otherwise indicated.

2.1.2 *Details of the procedure*

The following technique is adequate for the determination of melting point:

Grind about 50 mg of the substance to be tested in a small mortar. Place the ground substance in a vacuum desiccator over silica gel or phosphorus pentoxide at room temperature and dry for about 24 hours (unless another drying procedure is given in the test sheet). Place the substance in a dry capillary tube of 1-mm internal diameter forming a column about 3 mm high. Heat the melting-point apparatus to a temperature 5–10 °C below the expected temperature of melting and adjust the heating so that the temperature in the chamber rises about 1 °C per minute. Introduce the capillary with the substance into the heated chamber, and note the temperature when the sintered substance becomes completely transparent; this is considered to be the melting point, as defined in section 2.1.1.

2.1.3 *Discussion*

The difference between the purely theoretical definition of the melting temperature and the results obtained in practice is now widely recognized. A precise physical definition exists only for the so-called triple point, i.e., the temperature at which all three phases (solid, liquid and gaseous) are in equilibrium. The measurement of the triple point is done in a highly complicated experiment. Many compendia do not use this temperature, but describe melting intervals as observed in practice,