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GUIDANCE FOR THOSE PREPARING OR COMMENTING ON MONOGRAPHS FOR PREPARATIONS TO BE INCLUDED IN THE INTERNATIONAL PHARMOPOEIA

In preparing or commenting upon monographs for inclusion in The International Pharmacopoeia experts are asked to bear in mind the role and objectives of that pharmacopoeia, which have been summarized as follows:

- a) to provide specifications on the purity and potency of essential drug substances, widely-used pharmaceutical aids, and dosage forms. These specifications should be adequate to assure the safety and efficacy of these products, as well as adequate reproducibility of their effects in clinical use, but they should not be unnecessarily stringent, since this would increase the cost of the products. In the case of recently introduced products, specifications should be developed to ensure compatibility with the samples on which the toxicological properties and clinical efficacy and safety were initially established;
- b) to support such specifications with readily applicable methods of testing and analysis, with attention to the facilities available within control laboratories in developing countries;
- c) to provide general methods of analysis that would be applicable not only to materials included in the pharmacopoeia but also to new products submitted for registration;
- d) to accommodate, where appropriate, a measure of flexibility into methods and requirements that will facilitate the use of The International Pharmacopoeia on a global basis, particularly in connexion with dosage forms; and
- e) to present all these elements in such a manner that The International Pharmacopoeia, or selective parts of it, can be officially adopted by any Member State (of the World Health Organization).

To meet some of these aims guidance concerning monographs for drug substances has been published (WHO Expert Committee on Specifications for Pharmaceutical Preparations - twenty-ninth report, Technical Report Series 704). The additional guidelines set out below refer specifically to monographs for dosage forms.

1. Reference substances should be avoided if this is possible.
2. In those cases where infrared spectrophotometry is regarded as essential for the appropriate identification of a particular drug substance in a dosage form an alternative series of tests should always be given. Because the process of extraction of the drug substance from the dosage form may result in a polymorphic change, appropriate instructions should be given to ensure that the extracted ingredient is converted to the form on which any reference spectrum is based.

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3. In the alternative series of identification tests it is often useful to employ the solvent system of TLC where one is used in the test for related substances for identification purposes as well; this, however, requires a reference substance and it should therefore be invoked only if it has proved essential to establish a reference substance for other purposes.
4. It is desirable that at least one colour test should be included in the identification scheme. The combination of tests proposed should provide reasonable assurance that the contents of a container are consistent with the statement on the label.
5. Since The International Pharmacopoeia is intended to provide an independent challenge to dosage forms and since the analyst examining such samples may not have recourse to data obtained on the active ingredient used to manufacture the dosage forms it is considered desirable that tests should be included in the monograph for the dosage form to demonstrate freedom from undue quantities of manufacturing or degradation impurities. Tests for impurities that may arise in the synthetic process used to manufacture the drug substance serve to demonstrate that an acceptable quality of that ingredient has been used to prepare the dosage form. Tests for impurities that may arise from degradation of the drug substance either during preparation of the dosage form or during its storage serve to demonstrate appropriate manufacture and storage. It should be recognized, however, that the limits for impurities arising from degradation of the drug substance during manufacture of the dosage form may often need to be less stringent than those for the same degradation that apply to the drug substance itself. Limits for impurities that may arise only during synthesis should, on the other hand, be of similar stringency to those applied to the drug substance itself.

Wherever possible impurities should be sought using thin-layer chromatography (high-low system) by applying a suitable solution prepared from the dosage form at a reasonably high loading and comparing any secondary spots obtained with the principal spot in the same solution appropriately diluted. Due regard should be paid, however, to the fact that in certain drugs the possible impurities may respond very differently to the system of visualization used. Such problems may be minimized by using for example, fluorescent plates and examining under an ultraviolet lamp having a maximum output at about 254 nm or iodine vapours to produce coloured spots. In general, it is desirable to choose a system such that the principal spot shows an R_f value of about 0.5, although in certain cases it can be of advantage if the principal spot remains near the baseline or migrates to the solvent front, provided that secondary spots of interest are well separated.

6. Gas-liquid chromatography or high performance liquid chromatography (HPLC) should be used only when there is full justification for doing so, i.e. where it is of particular importance to control an impurity and where no other method is reasonably available.
7. Heavy metals tests should be employed only when the dosage of the drug demands it, e.g., when quantities of 0.5 g or more are given per day over a long period, or when some other reason can be identified.
8. Where it is necessary to control the acidity or alkalinity of a preparation, pH measurement should be included if the material has inherent buffering properties; otherwise a titrimetric procedure should be recommended. In general, a test for acidity or alkalinity should be

required only when the preparation being tested does not show a marked buffering effect. Such tests are, in general, only required for injectable preparations or for solutions that will come into contact with delicate membranes (such as the eye).

9. Requirements for clarity of solution should, in general, be invoked whenever the preparation, either as such or after solution, is intended to be injected or is for ocular use or when the presence of an opalescence is indicative of the presence of an impurity or of degradation. Such a test should not be included in monographs simply for the purpose of controlling the presence of mechanically introduced dirt.

10. The assay procedure employed might either be stability-indicating or if non-specific should be supplemented by appropriate limit tests for degradation products. It may be possible to use less accurate methods than would be necessary for the drug substance itself since specifications for dosage forms take into account not only the purity of the chemical product but also the practical facts of industrial manufacture.

11. All tests should, wherever possible, make use of reagents that are already described in The International Pharmacopoeia. Toxic materials such as mercuric salts, benzene, reagents known to be carcinogenic, and other undesirable materials should be avoided.

12. In view of the possible usage of The International Pharmacopoeia in tropical areas, care should be taken to minimize the use of very volatile solvents, such as ether. This is of particular importance in devising mobile phases for thin-layer chromatography, since the composition of such phases is liable to change if volatile solvents are included.

13. Existing pharmacopoeial methods should be invoked wherever possible since these will have been examined widely whereas new suggestions will require verification in other laboratories and the resources for this may not always be readily available.

14. Until tests for microbial contamination are developed a statement should be added to the monographs of natural origin under additional informations: Attention should be paid to the microbial purity.

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