PART II: Points of view

Europe

H. S. GRAINGER
M.Pharm., F.P.S., F.R.I.C.

European Pharmacopoeia Commission

Summary

At the present time, pharmacopoeias concentrate on defining the active principle of a product, limits of impurities and certain *in vitro* tests such as disintegration and dissolution rate which have been thought, incorrectly in many instances, to predict absorption characteristics.

In future, tests must be developed which will more adequately predict bio-availability and these, with information comparing the blood levels and clinical effects of different preparations of drugs, must be available to the prescriber in a pharmacopoeia or other officially recognized compendium.

EVIDENCE has been accumulating during the past few years of differences in biological availability of medicaments reputed to be identical in composition. These differences appear to arise from differences in formulation and biological control and have given rise to a new science of biopharmaceutics. The term is intended to indicate the emphasis on the study of the biological behaviour of pharmaceutical preparations as a function of their formulation, the latter study having concentrated mainly on the chemical, physico-chemical and mechanical aspects of compounding medicaments to form pharmaceutical preparations suitable for administration. Considerable publicity has been given by certain pharmaceutical manufacturers purporting to show that their product sold under a registered trade mark has biopharmaceutical advantages over preparations of the same medicament manufactured elsewhere.

The prescriber has an interest in assuring that the product he prescribes will not only contain the correct medicament in the correct dose, but that the pharmaceutical form in which it is presented will ensure uniform therapeutic effect when administered to the patient.

Hitherto, pharmacopoeias have concentrated on defining the medicinal substance, prescribing appropriate limits for impurities, prescribing the methods of testing and, where appropriate, the method of assay.

It is not claimed that these standards will ensure that the substance manufactured by firm A will be identical with that manufactured by firm B. They do, however, ensure that both manufacturers will produce material having the prescribed minimal content of the chemically pure entity, as determined by an official assay method, and that the impurities inevitably present will not exceed the prescribed limits. These standards are established after a thorough investigation of the material concerned and give an assurance that it will always be of a quality suitable for transformation into pharmaceutical preparations.

In a comparatively small number of cases the pharmacopoeia has prescribed biological tests for activity, for example vaccines, immunosera, insulin preparations, certain hormones such as corticotrophin, and tests of microbiological activity for antibiotics. Indeed it is difficult to see what value a monograph would have in such cases without such biological tests. The U.S. Pharmacopoeia, the British Pharmacopoeia and the Nordic Pharmacopoeia include also a considerable number of monographs on pharmaceutical preparations, particularly on tablets and capsules.

Most of the pharmacopoeias of the European countries, apart from those just mentioned, have very few monographs on particular pharmaceutical preparations and these are very limited in their scope. Examination of the monographs would give the impression that the pharmacopoeia has discharged its duty when it ensures: (a) that the tablet or capsule contains the stated medicinal substance; (b) that the quantity of medicinal substance is within the prescribed limits of tolerance; (c) that the tablet or capsule will disintegrate in the conditions prescribed in the test for disintegration; and (d) that, within tolerated limits, the tablets or capsules are uniform in weight. It has been assumed that a satisfactory disintegration test is an indication that the medicament will be released within a short time (say 15 or 30 min) in the stomach or intestine and

thereafter that its pharmaco-kinetic behaviour will follow physiological principles. It is now known that this is not the case, particularly when the medicament has a low water solubility or a poor partition coefficient with lipids, or where the excipients used in the manufacture of the tablet or capsule may interfere with the uptake of the medicament in the body fluids or on the mucosae of the intestinal tract.

Prescribers, being aware of the biological differences which may arise from these differences in the technique of manufacture, and being subjected to a good deal of publicity from manufacturers, are naturally anxious that the preparations they prescribe should provide reliable and uniform therapeutic effects.

The basic function of a pharmacopoeia is to publish, for the information of all concerned, the legal requirements as to the quality of the principal medicinal substances in use. It does this with a view to: (a) suppressing fraud; (b) eliminating error; (c) removing ignorance; and (d) ensuring adequate care during preparation. Insofar as the monographs of a pharmacopoeia fail to take note of variations known to constitute a risk to the patient, they are failing to fulfil their function. It is because of the known complicated nature of biopharmaceutical studies that many national pharmacopoeia authorities have refrained from including monographs on certain pharmaceutical preparations. In these circumstances control of the preparations concerned depends upon legislation, which has now been introduced in practically all countries, which requires an examination by an expert committee of confidential information submitted by the manufacturer to the registration authorities before the preparation in question can be released on the market.

There is no doubt that the manufacturer of a new medicinal substance is obliged to spend a considerable amount of time, effort and money on research and development of the preparation; visits to the manufacturing laboratories of the principal pharmaceutical houses readily reveals the intense care which is taken in these matters. It is therefore understandable that prescribers have greater confidence in preparations sold under the trade mark of a known manufacturer than they have in the case of the same medicament marketed under its official non-proprietary name from a house unknown to the prescriber.

When the preparation concerned is marketed only by one firm such confidence is probably justified because the manufacturer concerned has accumulated a great deal of experience which is not available elsewhere. It should be borne in mind, however, that the extensive pharmacological and biopharmaceutical tests which are the subject of submissions to the registration authorities, are carried out only

on the early batches of the preparation used in the pre-clinical and clinical testing stages.

My impression in discussions with many manufacturers is that it is not possible to carry out biological availability tests in humans on each production batch. For this reason, recourse is made to model tests such as the dissolution rate or the partition rate between aqueous and organic solvent phases which purport to reflect the performance of the preparation when administered to the patient. It can, nevertheless, arise that small changes in the technique of formulation or compression during routine production introduce different pharmaco-kinetic effects; a notable example is the recent case of digoxin tablets which received much publicity in the British press. An earlier notorious case was that of the particle size of griseofulvin. If formulation changes leading to important differences in biological availability such as these can arise within the laboratories of one manufacturer of a branded article, the risk of variation is very much greater when the same medicinal substance is manufactured by several manufacturers, each using his own trade mark. It is thus apparent that the mere fact of being sold under a trade mark (i.e. as a proprietary preparation) is no guarantee of biopharmaceutical uniformity.

In present circumstances many important medicinal substances are marketed by a multiplicity of manufacturers. This occurs when the patents of the substance itself have reached expiry or when voluntary or compulsory licences are granted to other manufacturers to make the same preparation. The same situation may arise in the case of a substance which for some reason cannot be patented. For example, the Extra Pharmacopoeia (Martindale) list nineteen proprietary brands of meprobamate and seven different brands of phenindione; there are eight different brands of tolbutamide, and so on. The problem of the multiplicity of trade names for preparations of the same medicinal substance is well known.

At a recent conference of the International Federation of Pharmaceutical Manufacturers Associations, a graph was displayed showing the differences in blood sugar levels obtained in patients after treatment with tolbutamide of different manufacture. The product showing the 'best curve' was nevertheless considered to be a dangerous product because the action was too rapid and intense, with obvious risk of hypoglycaemia. This gave rise to discussion about what was termed 'competitive advertising', in which the advertiser presents comparative data between his own and competitors' products. It is unlikely that a manufacturer would publish such comparative information if it did not show the advantages of his own product. Such information is therefore selected and biased and is

consequently misleading to the prescriber. In these circumstances it is difficult to say with certainty and as a matter of principle that branded products are necessarily superior to unbranded products, provided that the controls applied to the latter are adequate.

The disadvantage of insisting upon the branded product of the original manufacturer is that this creates a monopoly of the market for that particular substance. Public policy, for obvious reasons, has always been against uncontrolled monopolies, and this is particularly important in the case of medicines where the patient does not have the knowledge on which to make a choice. Even the patents law provides for compulsory licensing when this is in the public interest, precisely in order to avoid a monopoly situation. Further, the Trade-Marks Act is not intended to give a monopoly over a given substance to the owner of the trade mark but only to enable him to identify his products from those of any other manufacturer. In principle, therefore, the mere existence of the trade mark does not provide a guarantee of uniformity of therapeutic effect for a given medicament. Nevertheless, one has to admit that the conditions of manufacture of unbranded preparations may not be as carefully controlled as those of a branded product and particularly those of the originator of the product. On the other hand, some manufacturers of non-branded products do take very considerable precautions within the knowledge available to them or arising from their own development research, to ensure a satisfactory product. It would be unfair to conclude without real evidence that unbranded products are necessarily inferior to branded products. Such evidence is not easy to establish unless the criteria for the products in question are publicly declared, for example in a pharmacopoeia.

Some progress towards the ensuring of satisfactory conditions of manufacture has been introduced in recent legislation based on a Council of Europe Agreement on Quality Control, e.g. the Medicines Act in the U.K. and corresponding legislation which is to be found in all the main pharmaceutical manufacturing countries. This legislation requires not only adequate quality control at all stages in manufacture, but also provides for inspection of the manufacturing laboratory and the issuing of a manufacturing licence for each commodity. Nevertheless, one cannot say with certainty that the details of the control required are always identical with those applied to the original product. This is true both for competitive 'brands' and for non-branded products. To the extent to which such controls are inadequate there is failure on the part both of the registration authorities who grant the licence to manufacturers, and of the compendia of standards

such as the pharmacopoeias which establish the criteria which the product must satisfy.

I am expressing a personal view, and not necessarily that of the European Pharmacopoeia Commission or its various experts, when I say that I believe a fundamental change of concept is necessary in pharmacopoeias in the light of new knowledge and experience which has been accumulating in the last 10-15 years. I believe that the pharmacopoeia, which is a book of legal standards, plays an important role in establishing justice in the sense that it purports to provide a safeguard to the health of the patient using the medicament, and secondly, because it is a public document as distinct from a confidential dossier and thus ensures that justice is not only done, but is seen to be done. Pharmacopoeias should develop and prescribe appropriate tests which can be applied to all batches of a preparation and which will reflect with a reasonable degree of confidence the expected pharmacokinetic behaviour of the preparation. At the present time the number of parameters which could be invoked for such purposes is limited and debatable. It is clearly impractical for a pharmacopoeia to define in detail the formulation for a given medicinal tablet; for example the excipients to be used, the physical or chemical characteristics of such excipients, the precise method of granulation or compression etc. To prescribe such details would frustrate the development of improved techniques and would put an intolerable burden of responsibility on the compilers of the monographs. The pharmacopoeia should, however, prescribe appropriate functional tests to be applied to the finished preparation. Determination of the dissolution rate appears to be the main test at present being studied in this connection. It is, however, of importance only in a limited number of cases, for example substances of low solubility such as the corticosteroids. Unfortunately, even this test is the subject of considerable debate. Quite small changes of technique, such as rate of stirring or a propeller shaft which produces slight turbulence during the test can cause significant variation in the results obtained. A satisfactory, generally agreed method still remains to be established.

I believe that a public compendium (either the pharmacopoeia or even a new type of compendium) should establish certain criteria for the guidance of prescribers. The British Pharmaceutical Codex has for many years included information about the actions and uses of drugs. This has been information concerning the pharmacological and therapeutic uses of the substances but has not been extended to cover biopharmaceutical matters. I would suggest that consideration be given to including information about the expected pharmacokinetic behaviour of

preparations, particularly those prescribed in solid form. For example, it should be possible to study the blood levels or urinary excretion levels, changes in heart rate, or time of duration of other effects, such as blood sugar at a given time after administration of a stated dose to a normal subject in prescribed conditions, for example fasting, etc. Methods for determining these effects, e.g. analytical techniques for blood- or urine-levels, etc. should also be given. This information should be based on extended pharmacological experience including human pharmacology. In our present state of knowledge it is unlikely that such information could be used as a legal standard in the same way that the present analytical requirements of the pharmacopoeia are used. It could, however, form a useful source of basic information to clinicians, and particularly to clinical pharmacologists. After a period in which sufficient experience had been gained it might then be possible to establish obligatory criteria on the basis of which a preparation could be considered as acceptable or not. In this way some uniformity could be brought about in the pharmaco-kinetic behaviour of a medicinal substance manufactured and marketed by different manufacturers whether under a trade mark or not.

The obvious advantages of the trade mark are:

(a) for the prescriber it provides some assurance of uniformity when the preparation is obtained from the same source; (b) commercial protection to the owner of the trade mark. The disadvantages are: (a) an unjustified confidence in the use of a trade mark when it is known that the same substance may be sold under many different trade marks, thus defeating advantage (a) above; (b) confusion to prescribers when the same substance is sold under a multiplicity of trade marks.

The introduction of increased controls of biological availability in the manner suggested would make it possible to simplify nomenclature and would give a greater degree of confidence to prescribers whilst still permitting the manufacturer to identify his product by the use of a trade mark. In my view, however, the trade mark should always be accompanied by a clear and prominent indication of the official name of the active substance in the preparation. The removal of the monopoly element, together with increased requirements to ensure satisfactory biological availability, would provide healthy competition between manufacturers whilst removing the present suspicions that non-proprietary competitors are produced in conditions deficient to some extent as compared with those of the original product.