

Brand Names in prescribing

The second in a series of
Office of Health Economics monographs
dealing with aspects of the
prescription medical market in Britain

With a foreword by Arnold Beckett

Office of Health Economics

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Contents

Foreword	5
Background	7
Considerations for the prescriber	11
Economic considerations	19
The present situation	22
Conclusions	25

Foreword

I am very pleased to be associated with an attempt to present a balanced view of the brand name/generic controversy and the associated field of bio-availability. Many have discussed these problems; scientists, politicians, industrialists, legislators, hospital pharmacists, physicians, and clinical pharmacologists. Some have contributed to these discussions because of vested interests, because of potential political advantage or because of prestige and pride. Sometimes much more heat than light has resulted from these controversies. Those sections of society mostly involved when different medicines containing the same drug are not equivalent, so that incorrect medication occurs, have not been able to make their voices heard for obvious reasons – they have not yet realised the problems which can occur when compliance with official standards does not guarantee in itself the quality of the medicine. Unfortunately, many physicians are not sufficiently aware that different medicines containing the same drug can give different effects and side effects in the same patient even if the characteristics of the patient are unchanged. Many of the problems for the patient are hidden from scrutiny behind the all embracing term 'inter-subject variation'. However, when some of the changed responses in individuals are examined after a particular drug has been prescribed, some of the dramatic effects have been shown to be due to the use of different medicines containing the same drug.

It is imperative in the interest of patients that any new medicines introduced to the market and purporting to be equivalent to existing ones should be established as being equivalent. Also, urgent attention must be given to examining many of the existing medicines in which bioavailability problems can be predicted from the nature of the drug or of the formulation.

Politicians who stress only comparative prices of pharmaceutical products to gain political advantage do so at their peril when they advocate a course of action which results in incorrect medication of sick people by substandard or non-equivalent products. Senior civil servants also cannot evade their responsibilities when they give advice to buy on the price of medicinal products without due attention to the relative quality of those products.

If patients understood fully some of the difficulties arising from the lack of therapeutic equivalence of medicines they would be exercising considerable pressure on politicians and on government departments. An analogy can be drawn to the use of domestic gas; if the pressure one week were correct and the next week were half this value, then the results would not be attributed to the variations in the domestic apparatus but to the true reasons; the

public response would be in no uncertain terms.

However, for medicines, the change in a patient's response to a particular drug in a medicine is usually attributed to a change in the patient rather than to a change in the medicine producing a difference in the rate of release of the drug; frequently neither the patient nor the physician knows that a different medicine with different characteristics has been used.

Similar arguments apply to the side effects of drugs. If government departments only monitor adverse drug reactions using the name of the drug contained in different medicines, then they are misleading themselves and the physicians when they give advice based on this information.

The problems would disappear immediately if all medicines containing the same drug and all different batches of these medicines on the market were identical in clinical, biological and therapeutic activities. This is the ultimate goal, but it is many decades away; in the meantime this monograph is important in indicating the general background to the brand name/generic name problem.

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Background history

Until the middle of the nineteenth century, trade in Britain and other developed countries consisted mainly of the sale and purchase of bulk commodities. These were broadly undifferentiated, largely unstandardised and they competed primarily on price rather than performance. Manufactured goods up to that time were usually the individual products of specialist craftsmen.

During the past hundred years, however, the whole structure of industrial organisation has changed. Large companies and whole new industries have grown up as a result of mass production techniques.¹ In order to secure the necessary volume of sales, these new industries developed goods which were differentiated from their predecessors by innovative novelty, by consistency of quality and especially by branding and advertising. To survive under this new pattern of trade – whose development has coincided with dramatic advances in the range and quality of goods available to the public – companies must depend on successful research and development, on patent protection, on brand names, and on effective sales promotion. The customer in turn has come to rely on the advertised brand name as an indication of exactly what he or she is buying. It serves as an identification of the specific nature of the goods and as an assurance that the manufacturer has staked his reputation on their quality.

This revolution in the pattern of trade has applied to prescription medicines as well as to other classes of goods. However for medicines it has an additional significance; their brand names can play an important role in medical practice which is discussed in this paper. Despite this, however, pharmaceutical brand names are often more criticised and misunderstood than those of other products.

Part of this problem has arisen because the history of pharmaceutical brand names has differed somewhat from that of brand names generally. During the nineteenth century 'patent' medicines, which were often elaborate and misconceived nostrums, started commonly to be sold in the market place under fancy trade names. These preparations took the place of the earlier homely village remedies at a time of rapid urbanisation following the industrial revolution. A few of these patent medicines were excellent and have survived until the present day as useful branded household medicines; but the great majority fell into disrepute during the first half of the twentieth century and at least in Britain normal commercial pressures backed by successive Acts of Parliament

have driven most of them off the market.

However the mantle of disrepute associated with the 'brand names' of these nostrums failed to die with them.² It tended instead to fall onto another new class of medicines, the so-called 'ethicals', which were the direct lineal descendants of the potions first concocted by Galen before the year 200. These 'ethicals' were branded medicines which were elegantly compounded by wholesale manufacturers from high quality active ingredients, usually of vegetable origin. Many had a more or less useful pharmacological action (even if it was due only to the alcohol contained in their tinctures) and they were advertised exclusively for the medical profession to prescribe and never direct to the public. Although their advantages were often confined to their elegance of formulation and to their consistency of composition, these branded prescription medicines were usually very much more expensive than the traditional Galenical preparations listed in the pharmacopoeias. Hence the popular opprobrium formerly attached to the nineteenth century hucksters' 'patent medicines' tended to persist for these expensive 'ethicals'.

From the 1940s onwards these branded 'ethicals' gave way in turn to yet another new generation of medicines. These were the products of the new chemotherapeutic revolution which started in the late 1930s and 1940s with the sulphonamides and penicillin and led on in the 1950s and 1960s to a plethora of highly specific remedies for a whole range of previously untreatable diseases. These were increasingly formulated from single pharmaceutical chemical entities so that these specific remedies gradually replaced the previously typical examples of elaborate non-specific polypharmacy. Although the single active ingredient was commonly referred to by its chemical name, the preparation containing it was normally advertised and prescribed under its manufacturer's brand name. In this situation, the arguments for and against brand names as opposed to official, non-proprietary or generic names are often obscured because the choice between them is confused with the difference between the name of

1 The growth of the Ford Motor Car Company in the United States and the establishment of a whole township in Britain based on the production of 'Sunlight Soap' are characteristic examples of the new type of industrial development which occurred in the late nineteenth and early twentieth century.

2 In some cases the nineteenth century terminology itself persisted surprisingly long. As late as the 1950s some 'Wholesale Chemists and Druggists' still kept the branded medicines which they stocked in their 'Patents' Department'.

the active ingredient itself and the name of the medicine containing it. Together with the historical background described above, this has given rise to the confusion over nomenclature which is discussed in the next section and which accounts for much of the irrationality in the debate over how doctors should prescribe.

Confusion of nomenclature

Starting first with the names used to describe the active chemical ingredient of a medicine, the least commonly used is the systematic chemical name. This is constructed to indicate the molecular structure as clearly as possible to other chemists. The following example, which relates to an antimalarial compound, will illustrate why this type of name usually remains obscure outside the chemical laboratory. In this case, the systematic name is 7-chloro-4 [4-(N-ethyl-N-2-hydroxyethylamino)-1-methyl-butylamino] quinoline sulphate. This is meaningful to an organic chemist but quite useless in the practice of medicine.

The second way in which this same chemical compound can be described is by using the official International Non-proprietary Name (or generic name, as it is more commonly called), which in this particular case is hydroxychloroquine. This is very much briefer and less clumsy, but like the systematic name, this generic non-proprietary name properly applies only to the active ingredient and not to a particular medicine.

However, confusion starts to set in at this point, because the medicine itself is also sometimes described by reference to its International Non-proprietary Name. This would commonly be done, for example, if tablets, ointments or injections containing the active ingredient are included in such books as the *British Pharmacopoeia* (BP) or the *British National Formulary* (BNF). These reference books will specify the type of preparation and also the quantity of active ingredient. A doctor could in this case, for instance, prescribe 'hydroxychloroquine tablets BP'. This would indicate to the dispensing pharmacist that the tablets must contain 200 mg of hydroxychloroquine and must have certain broad physical properties in order to comply with the brief specifications laid down in the *Pharmacopoeia*. It does not, however, indicate how the tablets must be formulated or even which particular substances should be added as excipients to the active ingredient during the process of tableting. Thus the International Non-proprietary Name may be used in two quite distinct senses. In the first it defines a *specific*

chemical (or drug) entity; in the second it describes a *generic* type of medicine.

Confusion is worse confounded because the same double usage can sometimes apply in reverse to the manufacturer's brand name. To pursue the same example, the manufacturer's brand name 'Plaquenil' specifies precisely his own formulation of tablets containing the chemical hydroxychloroquine. Whereas hydroxychloroquine tablets BP might be made in various different ways by different manufacturers, the owner of the brand name Plaquenil invariably formulates his tablets in precisely the same way. The significance of this is discussed in the later section on 'quality, bioavailability and therapeutic equivalence'. For the present it is enough to record that hydroxychloroquine tablets BP might vary significantly as between different manufacturers whereas Plaquenil tablets are always consistent in their composition, quality and pharmacological activity. Thus the brand name provides a convenient way of describing in a single word the active ingredient together with the precise formulation in which it is presented. However, just as the generic name is used to describe the medicine as well as the ingredient, so the brand name is sometimes loosely used to describe the active ingredient as well as the medicine. Thus doctors or pharmacists might refer to the active ingredient of a preparation as being 'Plaquenil'. In this case the brand name is being used to describe the chemical itself rather than the tablet or injection.³

Against this background, it is not surprising that discussion on the relative merits of the use of brand and generic names in prescribing has sometimes been ill-founded. Figure 1 attempts to summarise the situation which has been described so far in order to provide an intelligible basis from which to develop the arguments set out on the subject in this paper.

Broadly, the arguments in favour of a doctor prescribing by non-proprietary, generic or pharmacopoeial names are first that he is automatically made aware of the particular active substance which he is prescribing and second that, if appropriate, the pharmacist can dispense the cheapest available preparation. The arguments in favour of brand names, on the other hand, are those of convenience to the prescriber, of the

³ This usage was more common in the past, when for example hospital pharmacists might order a few grams of the active chemical under its brand name in order to prepare special injections or ointments from it to the specific formula of one of the hospital consultants. This practice has more or less died out, mainly because it is now recognised that satisfactory formulation may often be a highly complex matter.

1 How names for medicines can be used

Type of name	Systematic chemical name	Official; International Non-proprietary; unbranded or generic name	Brand name
As applied to the 'drug' or active ingredient	Describes chemical composition and structure	Commonly and properly used to describe the active chemical or drug	Can be used loosely to refer to the active chemical substance made by a particular manufacturer
As applied to the medicine	Not used	May be used in conjunction with a physical description (e.g. tablets) and work of reference (e.g. <i>BP</i> , <i>BNF</i>) to describe a formulation of the active ingredient in general terms only	Describes precisely the medicine as made by the one specific owner of the brand name

elements of scientific precision and safety implied in specifying one particular formulation, and of their economic importance to the manufacturers. Before delving into the controversy arising from these two sets of arguments, it is useful to dismiss a number of special cases in which they are largely irrelevant.

The special cases

The most obvious special case in which the argument between the relative merits of brand and generic names is irrelevant is with a special formulation produced by one manufacturer with the deliberate intention that it should have a precise and unique therapeutic action as a result of its particular pharmaceutical characteristics. Examples would be sustained release capsules, aerosols, special ointments and some of the latest medicines formulated so as to deliver the active drug directly to its site of action. In these cases the formulation of the medicine and its mode of action are specific to the manufacturer's own preparation, whether or not the active ingredient itself is available from other sources. These products can only be properly identified either by the use of their brand name or else by a cumbersome phrase identifying the ingredients, the specific nature of the formulation and the manufacturer. In such cases the former of these two alternatives is generally agreed to be preferable, and the advantages from the use of the brand name are not in dispute.

Another similar case can arise with medicines containing a combination of two or more active ingredients. Some 'standard' combination products such as 'compound tablets of codeine' are listed in the pharmacopoeias or formularies. If manufacturers also sell these same combinations under their own brand names, the situation is no different from the case of a medicine with only a single ingredient. Doctors can prescribe the particular quantitative combination of ingredients (but not, it should be noted, any one particular formulation of these ingredients) either by their generic or brand name. However, if on the other hand a manufacturer produces a medicine in which the combination of active ingredients is unique to his own brand of tablet or mixture and is not included in any formulary, once again the only convenient way to identify the medicine is by its brand name.

The last case in which the general issues concerning the relative merits of brand and generic prescribing are less relevant is probably the commonest. This is where a branded preparation contains one or more active ingredients which

are covered by patents and hence can be manufactured by one firm only. Obviously, in such cases the same tablets – those of the exclusive patent holder – will be dispensed whether the doctor uses the brand name or not. They are the only ones available. The arguments about potential economies from the dispensing of cheaper generic preparations and the arguments about the risk of therapeutic differences between preparations of the same active ingredient manufactured by different firms both therefore become irrelevant. The other arguments, first, about the convenience of the brand name for the prescriber and, second, arising from the automatic awareness of the active ingredient implicit in using generic names do, of course, still apply.

Considerations for the prescriber

From the historical background outlined in the introduction to this paper, it is obvious that the entire pattern of therapeutics has been revolutionised over the past 25 years. Up to the 1940s, doctors were still largely dependent on traditional Galenical preparations in one form or another. With some notable exceptions, such as digitalis and cascara, their therapeutic use was often empirical and their activity relatively unspecific. Prescribing, like much of medicine in those days, was predominantly an art rather than a science.

Now, however, the vast majority of prescriptions are made out for single pharmaceutical chemical entities (or precisely standardised biological substances). These generally have a highly specific, if also highly complex, pharmacological action. In response, prescribing now needs to be as precise a science as possible, taking account of all factors which are likely to affect the therapeutic outcome of the medication. It is in this context that the use of brand names has assumed a new significance.

Quality, bioavailability and therapeutic equivalence

As has been pointed out, the choice between prescribing by brand or generic name raises broadly three questions for the prescriber: convenience; the importance of understanding the rationale behind the type of therapy he selects for his patient; and the central issue of how confident he can be that his patient is receiving precisely the medication which was intended. This section of the paper discusses in detail this third question; the following section deals with the other two. Returning to the era of the Galenicals, it was generally assumed that a given dose of active ingredient would produce a standard therapeutic response in a particular individual. The same was still assumed to be true when these Galenicals were replaced by mass produced tablets (and the other preparations) based on specific pharmaceutical chemical entities. Up to the 1960s, it was only for the biological preparations, such as vaccines, that routine assay and standardisation of therapeutic activity was considered necessary. For all other preparations, a chemical assay to ensure that they contained the correct amount of active ingredient was considered sufficient. In the 1960s, however, the highly specific therapeutic effect expected from the new pharmaceutical chemicals caused physicians to notice variations in patients' response occurring with different medicines containing the identical dose of the same active ingredient.

Pharmacists and physicians started increasingly to discuss this newly observed phenomenon under the heading of 'bioavailability'. But it was not until the 1970s that its significance was forcibly drawn to the general attention of prescribers in Britain by the 'digoxin episode', which is discussed below.

As a result, it is now generally realised that the way in which the active ingredient is formulated into the final medicament can in some cases very substantially affect the way in which the patient responds. In other words, the pharmacological action of a medicine cannot be predicted only in terms of the nature and quantity of active drug which it contains; it may also be significantly affected by the formulation. This important difference between the 'drug' itself and the 'medicine' containing it has been explicitly described by Beckett⁴. His diagram shown in Figure 2 illustrates the process involved in converting the drug into a medicine. During this process many factors may be introduced which will cause variations in the therapeutic activity of the final medicine. Figure 3, for example, sets out 32 of these factors which Sadove and his colleagues⁵ listed as being potentially significant. The consequent distinction between a particular medicine, on the one hand, and a generic preparation for which only the active ingredient is specified, on the other, has been officially recognised under the National Health Service in Britain. In his evidence to the 1972-73 session of the Parliamentary Committee on Public Accounts, the then Permanent Secretary to the Department of Health and Social Security, Sir Philip Rogers, stated that 'the same constituents of a drug made up in a different way may have a different effect on the patient'. He explained that for this reason his Department no longer considered it to be a meaningful exercise to compare the costs of differently formulated 'alternative' medicines, even if they had equivalent drug constituents. The same point has also been recognised internationally. The *World Health Organisation Chronicle* in 1973 (27, 89) stated that 'Different formulations of the same drug may vary in their bioavailability to a clinically relevant extent, and there may be variations between batches as a result, for example, of minor changes in manufacturing procedures. Drugs from different sources should, therefore, be considered as distinct

4 Beckett A H (1974). Prescribing and the regulation of formulation. *Postgraduate Medical Journal*, 50, 125.

5 Sadove M S et al (1965). What is a generic equivalent? *American Professional Pharmacist*.

2 Stages in the conversion of a drug into a medicine by formulation

Drug (Active principle)	Formulation (Addition of other materials and compounding)	Medicine (Pharmaceutical preparation or product)
Quality: compliance with official standard guarantees quality	Standardisation of materials, methods and manufacturer is important	Quality: compliance with official standards alone DOES NOT guarantee quality

Source: Beckett op cit

3 Some of the factors that can markedly alter the pharmacological action of a drug

1 Size of crystal or particle, its forms, and isomers.	16 Quantity of active ingredient. Relative and absolute.
2 Form of the agent – solution versus salt and type of salt.	17 Contaminants.
3 Vehicle (primary and secondary) excipient and/or binder.	18 Allergenic substances (primary and secondary) in product.
4 Coatings, number, and types.	19 Irritation.
5 Degree of hydration of crystal or addition of dehydrating substances to package, or hydration of diluents, vehicles, etc.	20 Melting point.
6 Diluent.	21 Ionisation of ingredients.
7 Purity – type and number of impurities.	22 Surface tension – surface active agents.
8 Viscosity.	23 Storage factors. Time, heat, light, vibration.
9 pH.	24 Flavouring and colouring agents.
10 Sustained release forms.	25 Dose or quantity of drug, its distribution and size of tablet or surface-to-tablet ratio.
11 Enteric Coating.	26 Type and characteristics of gelatin capsules.
12 Solubility.	27 Antioxidant included in preparation.
13 Vehicle, base, or suspending agents.	28 Dissolution and disintegration rate.
14 Container – stopper, type of glass, whether or not glass is pre-heated or impervious.	29 Buffer type and amount.
15 Package, dating, type, literature enclosed, dehydration of cotton in package – amount of cotton.	30 Air, mould or bacterial contamination of product.
	31 Antibacterial preservative.
	32 Metallic contamination in process of manufacture or in packaging.

Source: Sadove *et al*/ op cit

products or formulations whose equivalence can not be assumed on the basis of present pharmacopoeial standards.⁷

Some of the items listed in Figure 3, for example contamination with allergens, may increase the probability of 'side effects' or adverse reactions. Others, such as failure to protect against oxidation or ionization, may gradually reduce the overall potency of the medicine as well, perhaps, as increasing its toxicity. Ever since the days of the 'ethical' Galenicals, some of these and other similar aspects of quality in pharmaceutical formulation have been one of the traditional justifications for the higher prices charged for branded medicines. Just as with other classes of goods, the manufacturer's brand name stands as an assurance that the medicine had been consistently and reliably formulated.⁶ These arguments relating to quality are still highly relevant and they continue to have special force in the case of biological preparations such as insulin and vaccines. For these, variations in the standards of purity may have a dramatic impact on patient response. Tiny traces of foreign proteins, for example, may cause serious local reactions in susceptible patients if these impurities are allowed to remain in the final preparation. However, the last stages of purification to remove them may be extremely expensive, and may in themselves necessitate a substantial premium price for the brands concerned. Similarly, variations in the strains of organism used by different firms to produce vaccines against the same disease can greatly affect both the degree of protection afforded and the probability of adverse reactions.

However, the traditional importance of pharmaceutical purity and quality, which in itself could often justify a doctor's reliance on a branded prescription in preference to a generic one, has to some extent been overshadowed by the more recent considerations of 'bioavailability'. These introduce the very much wider range of factors which are covered in Figure 3. It is now realised that the differences in patient response already referred to may occur, for example, through variation in the particle size of the active drug, in its solubility or in the excipients which are combined with it. The consequences for the patient from the resulting variations in bioavailability are illustrated in Figure 4. For each of the preparations A, B and C, the same total quantity of active drug is eventually released. However, its rapid availability from preparation A may result in an early toxic response; whereas its slow sustained release from preparation C may

prevent its ever achieving a therapeutically effective plasma concentration. In this example, only preparation B would produce an effective therapeutic response without the risk of adverse reactions. For the other two preparations their pattern of bioavailability would make them significantly inferior despite the fact that they contained and eventually released precisely the same quantity of the active drug.

Such differences in patterns of bioavailability have been shown to present very real problems in practice. One classic case arose when it was found that patients with Addison's Disease at University College Hospital, London, were no longer being satisfactorily controlled by their treatment with cortisone. It was discovered that a change in the source of supply of tablets had been responsible. Although the new supplier's tablets complied satisfactorily with the pharmacopoeial standards they did not have the expected effect in patients. The poor bioavailability of their active ingredient resulted in a therapeutic response which fell far short of that achieved by the original supplier's tablets even though they contained the identical dose.⁷ A similar potentially calamitous example occurred in the treatment of diabetes in Canada.⁸ Here patients who had been responding satisfactorily to one manufacturer's brand of the oral antidiabetic tolbutamide were dispensed tablets from another source instead. Their failure to maintain the previous satisfactory control of their disease was found to be caused by a difference in the formulation of the tablets and hence in their therapeutic activity.

Another typical example where a change in formulation had a significant effect, although without, in this case, having life-threatening consequences, was the case in which it was possible, because of a reduction in particle size, to halve the content of griseofulvin in one manufacturer's ointment without affecting its therapeutic activity.⁹ Again this is merely one of many examples. The extensive literature recording many of the different aspects of bioavailability has been comprehensively

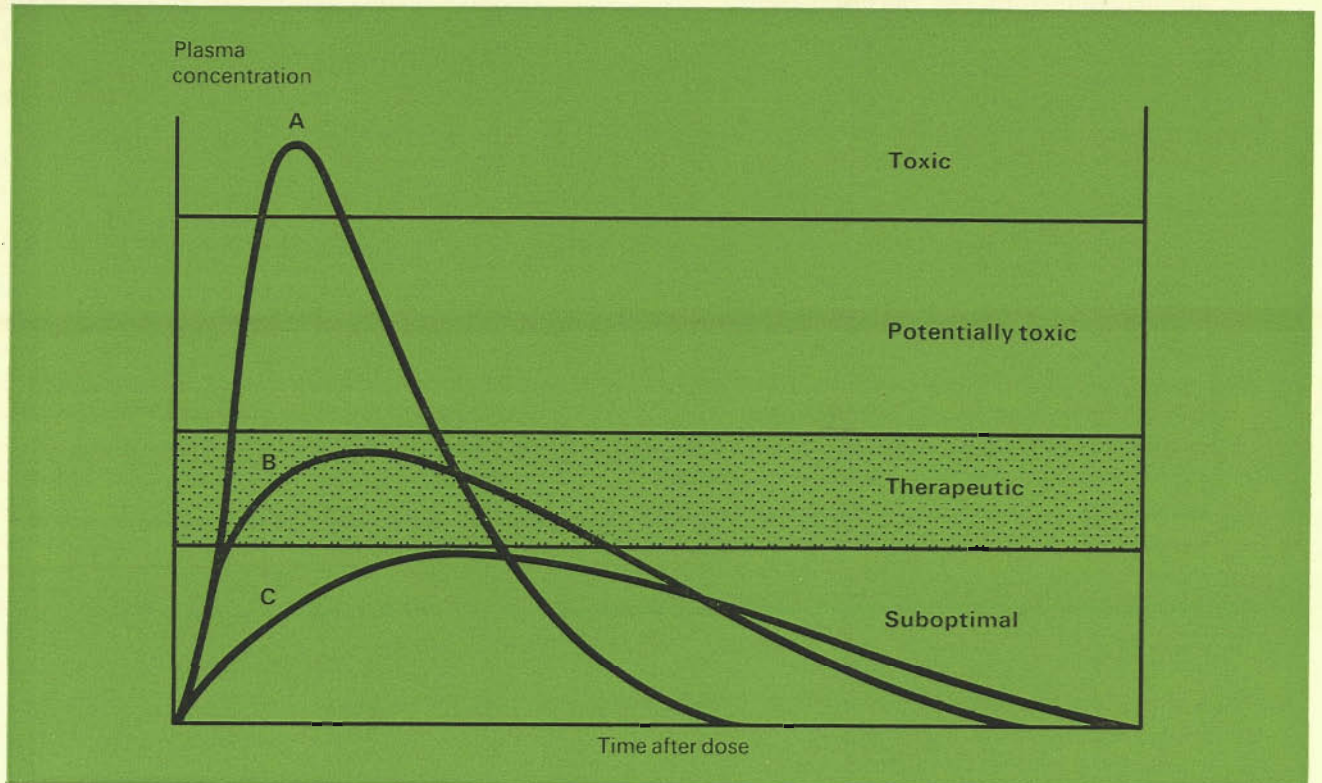
6 It is important to emphasise in this context that the formulation of a branded medicine must only be altered if prescribers have been carefully advised of any possible effects on therapeutic activity. Cases where it has been modified without notification to the prescribers could, if repeated, seriously undermine their faith in brand names generally.

7 Whittet T D (1971). Formulation and drug action. *Prescribers Journal*, 11, 48.

8 Carter A K (1963). Substitution for brand-named drugs. *Canadian Medical Association Journal*, 88-98.

9 Lees K A (1963). Pharmaceutical aspects of fine particles and their evaluation. British Pharmaceutical Conference.

4 Influence of rate of drug delivery from a medicine on therapeutic activity



Source: Beckett op cit

reviewed in Britain by Florence.¹⁰ His paper contained over 80 references and Figure 5 lists 43 compounds for which it recorded problems of bioavailability.

Two diagrams will suffice to underline the potential magnitude of the differences in response which can be obtained in practice. Beckett¹¹, for example, has shown the differences in average serum levels resulting from an equivalent dose of antibiotic administered in three different oral dosage forms. Figure 6 shows that an aqueous solution gives a maximum serum level which is an order of magnitude greater than that achieved by a capsule of dry powder. This, in turn, will reflect the sort of difference which can result from differences in the rates of solubility of a drug in a medicament. Such differences in response following a single dose will, in addition, tend to be even more accentuated in cases where successive doses are given to build up an eventual 'steady-state' plasma level.

Figure 7 shows the practical consequences of a relatively minor reformulation of a brand of digoxin which has already been mentioned. The peak plasma level was almost trebled. This example caused considerable concern not only because it dramatically publicised the whole problem of bioavailability but also because it brought to light for the first time the enormous variations in therapeutic response which could occur with different brands of this particular drug.¹² To an extent, this provided an explanation for the frequently observed toxicity of digoxin in earlier medical practice. Indeed, such was the seriousness of the problem that until the *British Pharmacopoeia* had been amended to ensure closer control of the bioavailability from 'digoxin tablets BP' the Committee on Safety of Medicines and the Pharmaceutical Society of Great Britain laid down special policies for dispensing which they hoped would minimise unwanted variations in activity.¹³ It should be emphasised once again that these diagrams are merely two examples from a very large number of other similar ones which could have been illustrated. The concept of unpredictable bioavailability and hence of potentially dangerous lack of therapeutic equivalence is now well established in clinical pharmacology.

5 Drugs subject to biological availability problems

Acetohexamide
 Acetylsalicylic acid
 Aminophylline
 Bishydroxycoumarin
 Chloramphenicol
 Chlorotetracycline
 Diethylstilboestrol (stilboestrol)
 Digoxin
 Diphenyl hydantoin (phenytoin)
 Erythromycin
 Erythromycin estolate
 Erythromycin stearate
 Ferrous sulphate
 Griseofulvin
 Hydrochlorothiazide
 Hydrocortisone
 Indomethacin
 Isoniazid
 Levopropoxyphene napsylate
 Meprobamate
 Methandrostenolone
 Methylprednisolone
 Nitrofurantoin
 Oxytetracycline dihydrate
 Oxytetracycline hydrochloride
 Pentaerythritol tetranitrate
 Penicillin G potassium
 Penicillin V potassium
 Phenylbutazone
 Prednisolone
 Prednisone
 Quinidine sulphate
 Reserpine
 Secobarbitone sodium (quinalbarbitone)
 Sodium-PAS
 Spironolactone
 Sulphamethoxazole
 Sulfisoxazole (sulphafurazole)
 Tetracycline
 Theophylline ephedrine plus phenobarbitone
 Thyroid
 Tolbutamide
 Warfarin sodium

Source: Florence, 1972

10 Florence A T (1972). Generic Equivalence; a look at the literature. *Pharmaceutical Journal*, 208-456.

11 Beckett op cit (after J. G. Wagner).

12 It also demonstrated clearly that any reformulation of a particular brand must only be undertaken after full evaluation of the consequences for its bioavailability; this was not always previously recognised.

13 Shaw T R D (1974). The digoxin affair. *Postgraduate Medical Journal*, 50, 98.

Nevertheless, the case in favour of using brand names in prescribing should not be linked too closely to the subject of bioavailability alone. It is by no means of universal relevance. Indeed, to put the matter in perspective, Turner¹⁴ has conveniently categorised five situations in which differences in bioavailability from various formulations of drugs are likely to be of therapeutic significance:

(a) Sparingly soluble drugs such as digoxin, where there is a close relationship between dissolution rate and steady-state plasma level, and where formulation with similar disintegration times may show marked differences in their dissolution rates (Johnson *et al*, 1973).¹⁵

(b) Drugs with small therapeutic doses of up to 1 mg where variation in tablet content or availability might be expected to produce more marked effects. Individual tablet assay in quality control is desirable for drugs whose doses are 1 mg or less.

(c) In replacement therapy, such as for thyroid, and adrenal cortical deficiency, and in diabetes mellitus. The clinical effects of small changes in bioavailability of replacement drugs in conditions such as hypothyroidism and Addison's Disease may develop only slowly and insidiously, and may not, therefore, be easily recognised until a serious condition has developed.

(d) In the control of serious clinical conditions in which optimum drug blood levels fall within a narrow range, such as anticonvulsant and anti-dysrhythmic therapy. Changes in formulation of the anticonvulsant drug phenytoin, for example, have resulted in the development of phenytoin intoxication due to enhanced absorption of the drug (Tyrer *et al*, 1970).¹⁶

(e) Where the drug has a very narrow therapeutic ratio so that relatively small changes in plasma concentration may lead to failure of therapeutic effect or to the development of signs of toxicity. Digoxin, phenytoin and oral anticoagulants provide examples of such a situation.

These five categories, taken together with the list of drugs in Figure 5, cover examples ranging from cases where variations in biological availability can be fatal to those where rational and consistent therapy ceases to be possible if the precise pharmacological behaviour of the medicine (as opposed to the 'drug') cannot be predicted.

However, there are other cases, as with the mild analgesics and the antacids, where very substantial variations in bioavailability may have little or no

therapeutic significance. In addition, it has been shown that very large variations in individual human response may sometimes outweigh relatively smaller variations in bioavailability from different medicines. For these cases, arguments in favour of the use of brand names as a method of ensuring consistent pharmacological activity have limited validity.

However, on balance, in the present state of the art, considerations of quality, bioavailability and therapeutic equivalence do seem to militate in favour of brand name prescribing (or some other way of specifying precisely the medicine as opposed to its mere active ingredient). For at least a significant minority of prescriptions the unpredictability of pharmacological response resulting from the use of a generic name may have serious therapeutic consequences. More generally, it can be argued that even if brand names can do no more than eliminate one set of the elements of uncertainty (i.e. quality and bioavailability) from the therapeutic equation, their use can still improve the scientific precision of prescribing and thus enhance the quality of therapeutics as a whole.

Medical convenience and awareness

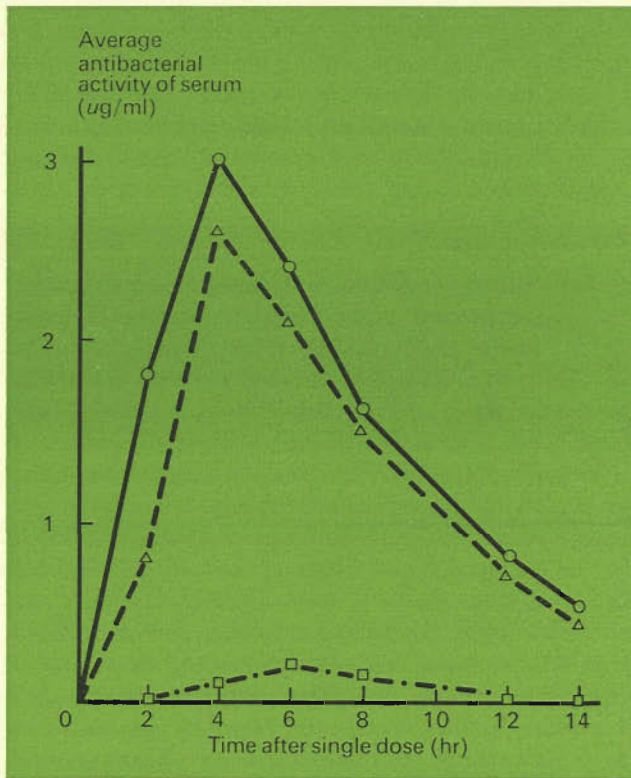
It has already been pointed out that the brand name is a convenient way of specifying the nature and quantity of active ingredients in a medicine together with its exact formulation. The brand name is usually shorter and more easily memorised than the official or non-proprietary name. More importantly, it identifies unambiguously the manufacturer (and hence the precise method of manufacture) in the same single word which indicates the constituents. If the prescriber wishes to indicate in any other way that the patient is to receive a medicine formulated and manufactured by a particular company he must write the more cumbersome official name in juxtaposition with that of the manufacturer. Returning to the original example of the antimalarial, he would need to write 'hydroxychloroquine, Winthrop' instead of the company's brand name 'Plaquenil'. Thus if the question of convenience were the only one involved the choice would invariably favour brand names. However, clinical pharmacologists have argued cogently that the use of brand names in

¹⁴ Turner P (1974). The clinical pharmacologist. *Postgraduate Medical Journal*, 50, 93.

¹⁵ Johnson B F, Gree H, McCrevie J, Bye C and Fowle A (1973). Rate of dissolution of digoxin tablets as a predictor of absorption. *Lancet*, i, 1473.

¹⁶ Tyrer J H, Eadie M J, Sutherland J M and Hooper W D (1970). Outbreak of an anticonvulsant intoxication in an Australian city. *British Medical Journal*, 4, 271.

6 Patterns of bioavailability from three formulations of antibiotic

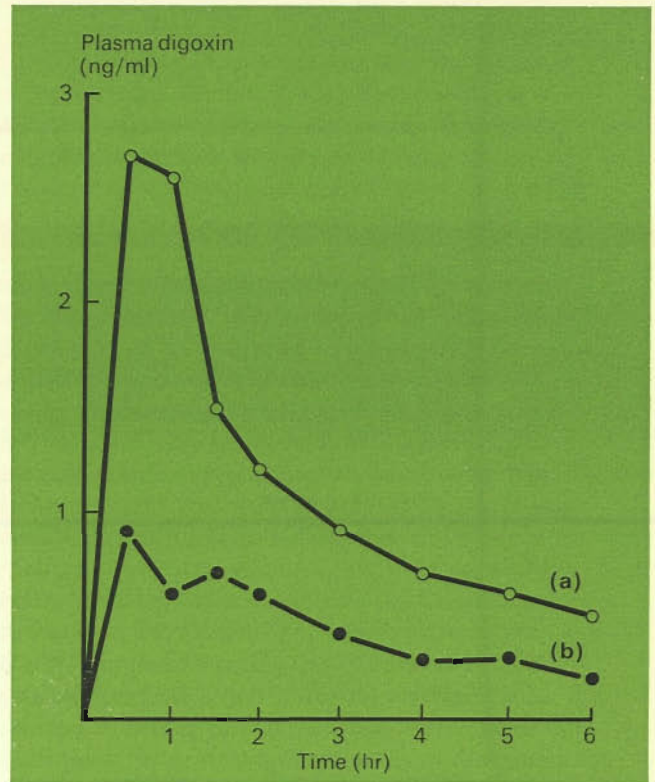


Equivalent single doses of an antibiotic administered orally in three forms. O—O, aqueous suspension of antibiotic derivative; Δ—Δ, aqueous solution of parent antibiotic; □—□, antibiotic derivative as powder in capsule without additives.

Source: Beckett op cit

7 Variations in bioavailability of digoxin

Absorption curves recorded in a normal subject after a 0.5 mg dose of Lanoxin manufactured (a) after the change of May 1972 (newer Lanoxin) and (b) shortly before this second alteration in production method (older Lanoxin).



Source: Shaw op cit

prescribing may not foster the same degree of pharmacological understanding as generic names. In the extreme case, a doctor may be unaware that two different branded preparations are both based on the same active ingredient. More generally, it is argued that brand names can conceal the therapeutic similarity between compounds from the same chemical or pharmacological 'family'. The non-proprietary names, on the other hand, tend to be chosen if possible so as to reveal such similarities. On this basis, it is argued that the use of generic names should help automatically to remind doctors of the general pharmacological activity of the substance which they are prescribing for their patients. This can be especially important for some categories of medicine. For example among the antidepressants there are several fairly clearly defined classes or 'families' of compound. Each of these has a distinct type of pharmacological action which is more or less unrelated to that of the others. The generic names of their active ingredients indicate fairly clearly to which class each belongs, while the brand names of the medicines containing them do not.

In such a situation there are two alternatives. The doctor may continue to use brand names because of their convenience and more importantly because of the considerations of biological equivalence which were discussed in the previous section. If so, he is under an obligation to be aware at least of the pharmacological class, if not by exact non-proprietary name, of the active ingredient which is contained in the brand he chooses. Alternatively, he may normally use generic names since these will serve as a more or less automatic *aide-mémoire* to the pharmacological basis of his prescribing. In the latter case, however, he faces the risk of therapeutic non-equivalence with preparations originating from different manufacturers. When treating patients for whom this may represent a serious threat, he must either depart from his generic prescribing practice or else he must specify the manufacturer's name in association with that of the active ingredient.

In this connection the Sainsbury Report in 1967, which was generally hostile to the use of brand names, nevertheless recognised that it could be dangerous not to specify the precise formulation (and hence the manufacturer) when prescribing. The Report therefore advocated the second alternative set out above. It proposed that the doctor should prescribe the active therapeutic ingredient by its non-proprietary name and should add where appropriate the name of the specific manufacturer. The Committee felt that the

inconvenience of this practice for the prescriber was justified by the greater degree of pharmacological awareness which would in consequence be forced upon him. They also implied that the cumbersome nomenclature involved would to some extent handicap manufacturers in promoting the sales of their products. The manufacturers were quick to point out in response that the Sainsbury proposals would to this extent negate the economic advantages of brand names which are to be discussed in a later section of this paper.

More significantly, critics of the Sainsbury Report pointed to a potentially fatal flaw in this particular recommendation. When a new medicine is first introduced it is normally protected by patents and hence available only from the company which has been responsible for its development. Thus, for example, even if Beecham had been denied the use of their brand name 'Penbritin' when they developed the first semi-synthetic penicillin they would nevertheless still have been its only manufacturer. Every prescription written under the generic name of 'ampicillin' would therefore still necessarily have been filled by the Beecham product. In this situation, prescribers could never have been convinced that they should write 'ampicillin, Beecham' instead of 'ampicillin' on its own. Ten years later, however, when the original Beecham patents expired, other ampicillin preparations formulated in a variety of different ways became available. At that stage the single word 'ampicillin' no longer specified a unique formulation as it had done over the whole of the previous decade. It is inconceivable that more than a few prescribers could, after so many years, have been persuaded to change their established prescribing habit and to write two words instead of one in order to ensure that their patients continued to receive the Beecham product. Hence the well-meaning intention of the Sainsbury Committee's recommendation would never in practice have been realised. The proposal to use a generic name coupled with the manufacturer's name in prescribing would in practice have degenerated into doctors using the generic name alone. Hence the situation which the Sainsbury Committee specifically deprecated would almost inevitably have arisen had their recommendation been adopted. It appears, therefore, that if prescribers are in practice to specify the manufacturer (and hence the precise formulation) as well as the active ingredients of a medicine they must continue to use the brand name.

Economic considerations

Any discussion of potential economies in prescribing needs to be put in perspective against the costs of medical care as a whole. In 1974, the total National Health Service expenditure on pharmaceutical services both in and out of hospital was £418 million. This was about 11 per cent of the total health service expenditure of £3,922 million. However, the question of whether this was too much or too little should be judged only in relation to the overall benefits achieved. Although the next section of this paper does look specifically at the direct potential savings to the health service from generic prescribing, it can be argued that this takes altogether too narrow a view. The real issues hinge on two much broader considerations. The first, which is directly relevant to the use of brand names, concerns the economics of pharmaceutical innovation as a whole. In this sense, because brand names are an integral part of the whole process of innovation and of improvements in quality, their costs are those of innovation and quality themselves. If doctors were still confined to prescribing the nineteenth-century Galenicals, pharmaceutical costs would indeed be only a fraction of those today. However, clearly medical care would also have been deprived of one of its major contributions to progress. No conceivable monetary savings from the avoidance of brand names could have justified such a situation. The second broad economic issue leads on from the first. Accepting that the pharmacological progress of the past three decades has brought immeasurable benefits, how wisely are its products used? How near do doctors come to the optimal pattern of prescribing for their patients? Clearly this is a subject well beyond the scope of a paper on pharmaceutical brand names. However, it is useful to remember that the question of whether a particular prescription costs too much or too little pales into insignificance when put beside the question of whether the prescription should have been written at all. It is possible that some of the criticisms of 'expensive' brand name prescribing are in reality veiled criticisms of the overall pattern of prescribing itself. If this is indeed the case, these criticisms need to be looked at in relation to the standards of effectiveness and efficiency in the health service as a whole. Put in this context, the pharmaceutical services would probably rank high in terms of cost effectiveness; but this cannot be a subject for this paper.

Direct savings for the health service

Returning to the narrow argument about potential savings from the avoidance of brand names in

prescribing, one immediately echoes the historical criticism of expensive and elegant ethicals sold at high prices under their brand names in the 1930s and 1940s. On this analogy, it is still often argued that branded prescription medicines today add greatly to the cost of the health service, because in any given situation the same active ingredients could be dispensed more cheaply under their generic names.

It is true that in the case of a few individual branded medicines there are very substantial potential savings to be gained if the prescriber writes the generic rather than the brand name and thus allows the cheapest available medicine to be dispensed. Five examples were quoted by Dr Cornah of the Department of Health and Social Security at a Symposium in 1973.¹⁷ These were imiprimine, phenylbutazone, paracetamol, tetracycline and oxytetracycline. Taking the actual volume of tablets prescribed by general practitioners in Britain in 1972 as a base, he showed that for the five preparations taken together the difference between the cost of the most and the least expensive alternatives amounted to just over £5 million. The total realisable savings to the health service were, however, much less than this because many doctors already prescribed by generic name or else prescribed brands which were cheaper than the most expensive. Based on the total expenditure on these five products for the year, the potential saving from the exclusive use of generic names fell to about £2.5 million.

However, these five preparations were atypical. All, apart from paracetamol, had recently emerged from their initial period of patent protection. Each was unusual in that it still had substantial and profitable sales at this stage in its life. The more usual pattern is for a product to have fallen more or less into disuse as a result of being overtaken by subsequent innovations before the expiry of its patent life. Furthermore, under the conditions of the National Health Service – with all the pressures which are applied to encourage economical prescribing – the potential savings from generic prescribing in these cases would be shortlived. In such cases, either the original manufacturer must reduce the price of his brand to remain competitive or else prescribers will gradually start to favour the cheaper alternatives. Clearly the gap between the theoretical maximum extra cost of £5 million and

17 Cornah G (1974). The Department of Health. *Postgraduate Medical Journal*, 50, 77.

the maximum potential savings of half that figure indicates the extent to which prescribers had already in these five cases drifted away from prescribing the expensive originals in order to economise in their overall prescribing costs. In fact the figure of £2.5 million for 1972 probably represented the great majority of the total potential savings to the health service from generic prescribing in that year. It is highly unlikely that there were many other products which would have added substantially to the figure.¹⁸ However, no overall figures are published, because it has been pointed out that estimates of the total savings to the National Health Service from 'generic' dispensing are now no longer considered valid by the Department of Health. But even in the unlikely event that Cornah's figures accounted for only half the total (and a 'guesstimate' of 90 per cent of the total would probably be more accurate) the potential savings from generic prescribing or dispensing in 1972 would have amounted to less than 2 per cent of the total pharmaceutical expenditure. The trivial proportion of total expenditure represented by such potential savings in earlier years was indicated by figures published by the Public Accounts Committee for 1964, at a time when the concept of 'therapeutic equivalence' was still generally accepted. The potential savings (which arose from a total of only 25 preparations) amounted to £443,000, or rather less than 0.5 per cent of the pharmaceutical costs. In that year also – as it has been suggested was probably still true in 1972 – only five products accounted for almost 90 per cent of the total possible savings.

There are, of course, other sources apart from the direct differences in price from which short-term savings might accrue from generic prescribing or dispensing. One of the most obvious would be in reduction of the range of stock which has to be carried at present in pharmacies. This would reduce the need for storage space and simplify ordering and stock control. However, once again, the magnitude of this problem, and hence the implied estimates of potential savings, have been greatly exaggerated. This exaggeration is probably due in some measure to another confusion in connection with brand names. This arises because a multiplicity of similar but chemically distinct new drugs must each be marketed under its own brand name as well as having its own non-proprietary chemical name. However, in these cases the elimination of brand names would obviously not reduce the multiplicity of different products, except in so far as it inhibited innovation

generally. Hence no unnecessary product duplication arises directly from the use of brand names in such cases.

As far as the genuine duplication of brands is concerned, the most recent British statistics come from a study carried out in 1967.¹⁹ Of approximately 2,500 branded medicines on the market at that time, when the brand name/generic debate was perhaps at its height, only 340 or 13.6 per cent were duplicates. (Brands were considered as duplicates merely if they contained the same active ingredient; no account was taken of the ratio of ingredients for combination drugs or of presentation form – tablets, injections, etc.). These 340 duplicate brands represented between them 139 preparations. Thus from the whole available range of branded pharmaceutical preparations in 1967 only 201 could be considered to be 'unnecessary duplicates' containing the same active ingredients as others already on the market. Hence the general argument that the use of brand names in pharmacy leads to substantial duplication and waste is misconceived. On all counts, leaving broader economic considerations apart, the direct costs arising from prescribing by brand names rather than by generic names appear to be very much smaller than is commonly supposed.

Economics of pharmaceutical innovation

However, it has been pointed out that these relatively small short term costs or economies for the health service from brand name or generic prescribing need to be set in perspective against the longer term consequences of the brand name system in pharmaceutical innovation as a whole. Their importance here stems from the modern pharmaceutical industry's total dependence on successful research and development. Over the past two or three decades international trade in pharmaceuticals has come to comprise almost entirely modern, relatively expensive research-based branded medicines. Older unbranded medicines which are by now long-established in the various national formularies can usually be adequately and cheaply manufactured in even the less developed local world markets. International world trade in these unbranded products is consequently negligible. The developed countries

¹⁸ For example, paracetamol showed a potential saving of only £100,000. There was no reason to have included that example while at the same time omitting any other product for which higher potential savings could have strengthened the overall argument.

¹⁹ Jones R H (1967). Private communication.

such as Japan, the United States and Western Europe, account for about 90 per cent of total world pharmaceutical exports and imports, and pharmaceutical trade between these advanced countries depends almost entirely on the products of the last 30 years' pharmaceutical research. Any abolition or restriction on the use of brand names could, therefore, seriously affect the continued growth of the research-based pharmaceutical companies and their contribution not only to therapeutic progress but also to their national balance of payments. For Britain this amounted, on account of direct trade alone, to a net £275 million in 1975.

There is little doubt that proposals to abolish pharmaceutical brand names, such as those of the Sainsbury Committee, have been predicated in part on the fact that manufacturers would find it much harder to gain medical acceptance for their new medicines without the use of brand names. Thus their abolition, or any severe restriction on their use, would act as a powerful brake on pharmacological progress by delaying the process by which older less effective medicines are replaced by later innovations.

More specifically, there are cases in Britain where companies are forced to rely entirely on their brand name in order to protect their innovation. In such cases the companies are for various reasons unable to protect the fruits of their research investment under the patent laws. Some of the special cases already referred to, such as the unique formulations of existing well-established chemicals, are cases in point. In some other cases, even a medically novel chemical entity or active ingredient may be unable to obtain patent protection under British law. Such cases arise with naturally occurring substances such as vegetable extracts and the penicillin mould or materials of animal origin such as insulin. Other cases arise because the chemical substance has previously been recorded in the scientific literature even though it has never been used in medicine.

An example of this last situation arose with the analgesic paracetamol, which has already been mentioned in connection with potential savings in prescribing costs. This was described in the literature in the early part of this century, although its therapeutic importance as a safe pain killer was not then realised. Hence when it was first introduced as a medicine in Britain in the 1950s it could not be patented and its manufacturer's brand name was the only protection available to the company which had invested in the research to demonstrate its therapeutic effectiveness and

which had decided to take the very substantial commercial risk of promoting its use on a large scale in medical practice. Had this brand name protection not been available, the company could not have hoped to recover the investment involved in its introduction. Thus the medical profession and the public would have been denied what in retrospect has proved to be a very valuable and widely prescribed medicine. The present interest in the potential merits of other older chemicals and in naturally occurring substances – L-dopa for Parkinson's Disease is a good example – serves to underline the fundamental importance of brand names in encouraging research and development in pharmaceuticals, especially in cases where patent protection is not available.

These specific examples of how the abolition of brand names might inhibit pharmaceutical innovation are, of course, important. However, the real significance of brand names in this respect stems from the wider considerations referred to earlier. For all classes of industrial products and in virtually all countries,²⁰ brand names are accepted as a legitimate form of 'industrial property' through which a producer can protect the fruits of his innovation and can give his customers an assurance of consistent quality. Brand names perform this function for prescription medicines also, and it has been pointed out that in relation to quality and bioavailability they have an especial importance for the patient in this case. Any restriction on brand names therefore implies a curtailment of therapeutic innovation and an undermining of one of the important bases from which the quality of prescription medicines has been established. The various devices which have from time to time been proposed as a means of circumventing the brand name system for prescription medicines will be discussed in the final section of this paper. For the present, however, it must be pointed out once again that brand names have for historical reasons become an important method of underpinning the economic system which has produced the therapeutic revolution of the past three decades. While the system remains in existence, prescribing by brand name continues to be one way of fostering pharmaceutical progress at what has been shown to be an almost negligible direct cost in relation to expenditure on the National Health Service as a whole.

²⁰ Even in the Peoples Republic of China international brand names can be registered in the same way as in Western countries.

The present situation

Britain

Against the background of the discussion so far, it is not perhaps surprising that general practitioners in Britain overwhelmingly prefer brand names in their prescribing. In 1973, in terms of value, about 95 per cent of medicines dispensed through the pharmaceutical services were branded. However, for the reasons already discussed, non-proprietary, unbranded medicines generally consist of older and cheaper drugs than those supplied under brand names. As a result, prescriptions dispensed as non-proprietary preparations accounted for a considerably higher proportion of total number than of total value. In 1973, 18 per cent of all prescriptions were dispensed as unbranded preparations; the other 82 per cent were dispensed using branded medicines.²¹ As Figure 8 shows, this represented the outcome of a steady rise from only 16 per cent in 1949. Hence over the past 25 years British dispensing has shown a continued and significant swing in favour of branded prescription medicines. Once again, against the historical background outlined at the start of this paper, this preference for branded medicines is unsurprising. In fact, however, not all of these 82 per cent were prescribed by brand name. The figure includes some prescriptions written by generic name but necessarily dispensed as a branded preparation because this was the only form available. (This situation was described in the earlier section on 'The special cases'.) It is, therefore, perhaps most significant of all that as many as 74 per cent of prescriptions in 1971 (the latest year for which the breakdown is available) were actually written by doctors using the brand in preference to the generic name.²²

In hospitals, prescribing is more closely influenced by the teaching of pharmacologists, which will be discussed in the final section. This almost certainly results in a greater emphasis on the use of non-proprietary names, but no precise statistics are available. It is interesting, however, that hospital pharmacists in Britain have recently been reconsidering their position in relation to the use of pharmaceutical brand names. In the late 1950s the whole issue of branded prescribing and dispensing was brought to a head when hospital pharmacists found that they could obtain supplies of broad spectrum antibiotics from unlicensed manufacturers abroad at well below the prices being charged by the original innovators for their own branded preparations. Because these were high priced products, the pharmacists could effect substantial savings by dispensing foreign unbranded tablets. Thus the practice of substituting the cheapest

available medicine even when a particular brand had been prescribed became generally accepted and in many cases officially encouraged. The recent evidence and debate on bioavailability, however, has made pharmacists much more cautious and few would now apply the principle of substitution indiscriminately. For the mild analgesics and perhaps even for some antibiotics it may still justifiably be practised. However, few, if any, authorities under the National Health Service would now encourage substitution of cheaper alternative pharmaceutical supplies on considerations of price alone.

Other countries

Several countries have in the past either had experience of restrictions on the use of brand names for medicines or else have attempted to impose such restrictions. In general their experience confirms the overall impression that the use of brand names in this field confers net benefits.

For example, in France until 1959 brand names as they are normally used were prohibited. Instead the exclusive use of a brand name was granted only after the manufacturer had proved the chemical novelty of the compound for which it was to be used. That is, the grant of a French brand name was in many ways the equivalent of the grant of a patent in other countries. The innovator had an exclusive right to the use of his brand name and all other manufacturers of the same compound were confined to using the generic or non-proprietary name. However, this system proved unsatisfactory, and in 1959 the generally accepted principle of the use of brand names was extended to medicines as well as other classes of goods. At the same time, new pharmaceutical chemical entities arising from manufacturers' research were able to be protected in the normal way by product patents.

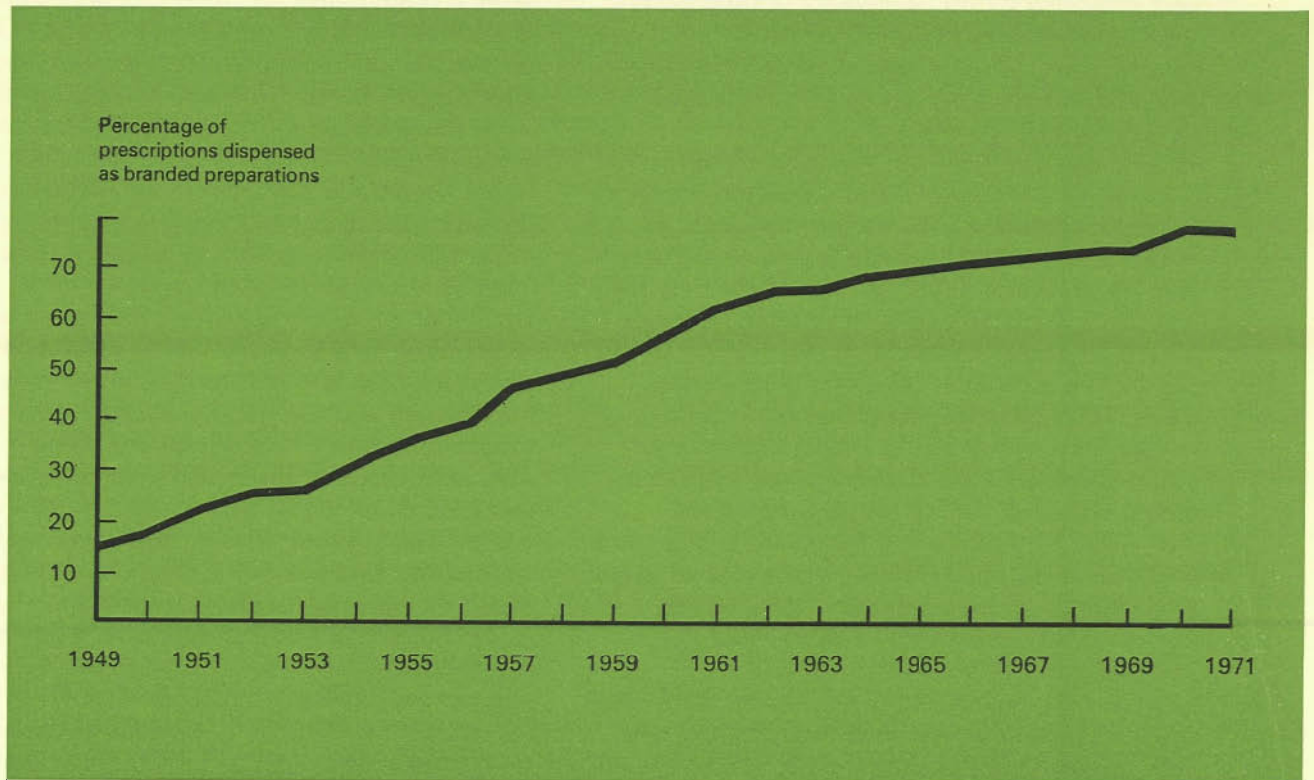
In accordance with its general economic policy, the Soviet Union also abolished brand names for medicines. However, once again by the 1950s severe disadvantages had begun to appear. The undifferentiated medicines from different state factories were found to be of uneven and unsatisfactory quality. At one time 75 per cent of samples examined by the Central Pharmaceutical Research Institute were being rejected.²³

21 HMSO (1974). Health and Personal Social Services Statistics.

22 Teeling-Smith G (1974). How doctors prescribe and why. *Postgraduate Medical Journal*, 50, 65.

23 *Medical Worker* (1961). Quoted in Bauer R A and Field M G (1962), *Ironic Contrast; us and USSR Drug Industries*. *Harvard Business Review*, 40, 5, 89.

8 Patterns of dispensing 1949–71



Source: Teeling-Smith *op cit*

Factories producing these inferior preparations were protected by the anonymity of their generic names. Satisfactory standards of quality were only restored when the principle of brand identification was reintroduced and factories were required to identify all their products.²⁴

More recently, other countries have attempted to abandon or undermine the brand name system for the identification of prescription medicines. In Pakistan in the late 1960s the government decreed that brand names could continue in use only for a very short list of medicines. This led to chaotic conditions and an extensive 'black market' for the original manufacturers' branded preparations which were often still illegally available from foreign sources.²⁵ Other countries in Africa and Latin America have run into similar troubles in their attempts to curtail the use of branded medicines. In Canada, the introduction of generic substitution together with the weakening of patent protection has been associated with a further decline in the already very limited Canadian pharmaceutical R and D.

Despite these experiences elsewhere, in the United States dispensing pharmacists in particular have been vociferously demanding more restrictions on the use of brand names. They have also been pressing for the introduction of laws to permit the substitution of generic products by pharmacists even when branded medicines have been prescribed. These demands appear to be based primarily on the claim that very substantial economic savings could be achieved. It is true that price differences between chemically similar medicines from different sources are sometimes greater in the United States than in Britain. However, it still seems probable that restrictions of brand name protection for pharmaceuticals would produce savings which would be negligible in comparison with those which could be achieved elsewhere in the Health Care System.

Historically in the USA, the post-war therapeutic revolution and the development of many relatively high-priced medicines by the large research-based pharmaceutical manufacturers encouraged smaller local firms without the same research overheads to enter the market with cheaper alternatives. From these early days, many US pharmacists favoured substitution because it could reduce their inventory problems as well as bringing economic advantages. The financial benefit from dispensing a low-priced substitute instead of the costly original could in many cases be shared between the ultimate customer and the pharmacist himself. However, State anti-substitution laws soon

quashed any movement in this direction.

More recently, however, there has been something of a reversal. During 1974, a study by the Office of Technology Assessment of the US Congress gave some support for the principle of drug substitution for 'interchangeable' drug products as one means of reducing the cost of tax-supported health schemes. In the light of this opinion and continued pressure from dispensing pharmacists, the anti-substitution laws were repealed, for example, in the State of Michigan in April, 1975.

Ever since 1970, the American Pharmaceutical Association (which represents the profession of pharmacy) has favoured generic prescribing and has officially committed itself to the repeal of anti-substitution laws.²⁶ The situation that the Association seeks is that when a doctor prescribes a medicine by its brand name alone the pharmacist will be free to substitute any other generically 'equivalent' preparation. Already in some States which do allow substitution, doctors must specify in their own handwriting that there is to be no substitution in order to be certain that his patient will receive the exact preparation which he thinks necessary. More recently, the total abolition of the brand name system for prescription medicines in the USA has been proposed. The Policy Committee on Public Affairs of the American Pharmaceutical Association has recommended the Association to 'undertake efforts including support of legislation to eliminate the use of brand names for prescription drug products'.

This present American position runs contrary to the trends which appear to be developing in other countries, where the importance of consistent bioavailability linked with the need to foster pharmaceutical innovation have provided the basis of growing support for pharmaceutical brand names. The US pharmaceutical industry is hopeful that in the near future the opinion of the American pharmaceutical profession will fall more into line with that in countries such as Britain.

24 Bauer R A and Field M G (1962), Ironic Contrast; us and USSR Drug Industries. *Harvard Business Review*, 40, 5, 89.

25 The situation has now partly been restored with the reintroduction of brand names at least for combination products.

26 Apple W S (1974). Current pharmaceutical juxtapositions in the USA. *Pharmaceutical Journal*, 213, 202.

Conclusions

This paper has examined the way in which pharmaceutical brand names fell into disrepute first through their abuse by nineteenth-century patent medicine hucksters and then because the high prices charged for the branded pharmaceutical elegance of the twentieth-century 'ethicals' seemed often to be unjustified. It has also set out a series of arguments for and against the use of brand names in prescribing today. On the one hand, they can add noticeably (although not monstrously) to the current cost of the pharmaceutical services. On the other, they form an important economic element in the whole process of pharmaceutical innovation. Again, they can provide an assurance of quality and, unlike the generic name, they give a precise specification of the pharmaceutical characteristics of the particular preparation. Against this, they can obscure the pharmacological basis on which the prescriber's choice of active ingredient (drug) should have been predicated. Finally, they are undoubtedly convenient to use. Clearly, no one of these arguments on its own can make an effective case for or against brand names; the situation needs to be viewed in its totality.

Furthermore, the paper has mentioned various alternative policies which have been suggested to obviate the need to use brand names. One example was the Sainsbury proposal for the prescriber to couple the generic name to that of the manufacturer. However, it has been explained that the effect of this would be little different from that of the unconditional abolition of brand names. Another proposal would be to give the original manufacturer the exclusive right for all time to the use of the official non-proprietary name. However, a modification of this has been tried and failed in France. Indeed, it is inevitable that it must in the long run stifle desirable competition. In effect, such a proposal grants the equivalent of a perpetual patent to the original innovator. Yet again, it has been argued that tighter and more comprehensive specifications in the official formularies could ensure all the necessary consistency in quality and bioavailability as between the products of different manufacturers. But this would need a massive extension of the bureaucracy in order to draw up very much more stringent official specifications for a vastly increased number of medicines. It would be an exceedingly costly, and probably unsatisfactory, way of eliminating the role of existing manufacturers' brand names. None of these various alternatives to the present system, therefore, appears to offer any obvious economic solution to the brand name controversy. Each of them, individually, would tend to retard

therapeutic innovation by the pharmaceutical manufacturers. It is pharmacological progress which is expensive rather than brand names in themselves.

On the other hand, much of the present antagonism towards the role of brand names in prescribing, and to some extent the reasons for their shortcomings in practice, seem to stem from the fundamental misunderstandings over nomenclature which were set out in the earlier part of this paper. The use of non-proprietary names in prescribing has often erroneously been assumed to be 'more scientific' than the use of brand names. This is true only in the sense that the prescriber automatically knows the official name of the active ingredient which he has selected. By using the non-proprietary name the prescriber will in many cases be selecting no more than a generic range of therapies for his patient rather than a specific medication; in this other sense it must be more scientific to prescribe the exact preparation by writing its brand name.

Perhaps the crucial misunderstanding arises because the pharmaceutical industry and the professions of pharmacy and pharmacology have failed to give a name to the latest generation of prescription medicines. A concept which has no name can never easily be grasped by those who are unfamiliar with it and this seems to be the situation with some prescribers and teachers of medicine in connection with the pharmaceutical brand name controversy. It is patently incorrect to call the type of medicines which have been discussed in this paper 'ethicals', although many informed people still do so. The term 'prescription medicine', on the other hand, covers both branded and generic preparations; and the term 'branded prescription medicine' is too cumbersome to be effective.

It is significant that particularly in the USA new pharmaceutical active ingredients which this paper (following the terminology of Beckett) has referred to loosely as 'drugs' are in scientific circles now generally called 'NCEs' – New Chemical Entities. What is needed is an equivalent name or rubric to describe the medicines which are formulated from these NCEs. One possible choice, from the discussion so far, seems to be 'pharmaspecifics'.

In a single word, pharmaspecific could be used to describe the concept of an active pharmaceutical chemical ingredient which has been formulated into a medicine in a precise and specific way by a particular manufacturer. Under this usage, the proper scientific way in which to designate a

particular pharmanespecific would be by using its brand name. This would correspond exactly to the equally proper scientific designation of an NCE or 'drug' by the use of its International Non-proprietary Name (INN). Perhaps it would lead to clarification if in due course the existing rather pejorative phrase 'brand name' could be replaced by the more descriptive phrase 'pharmanespecific name'. The latter would still be the exclusive property of its particular manufacturer, but the importance of its role in prescribing would be very much more explicit.

Clinical pharmacologists and pharmacists

Whether or not the term pharmanespecific gains general currency, there still needs to be a radical reconsideration of the attitudes towards existing brand names in the teaching of clinical pharmacology. Pharmacologists have in the past expressed very proper concern over the careless use of brand names in prescribing; that is, their use without proper consideration of the active ingredients which the medicines contain. In turn pharmaceutical advertising has been criticised because for defensive commercial reasons it has sometimes been forced to put undue emphasis on the brand name while at the same time playing down the name of the chemical ingredient. However, clinical pharmacologists have overstated their case when they have sometimes gone on to argue that brand name prescribing must be undesirable.²⁷ From the arguments in this paper it should have become clear that the two types of name serve a different purpose and to try to use one to fulfil the function of the other can be even more unscientific and potentially dangerous than misusing either of them in their proper context. If prescribers are encouraged to use generic names exclusively in their prescribing – on the mistaken assumption that they are invariably selecting a specific medicine for their patient – there must be some occasions when the patient may suffer seriously as a result. In this connection, it is also important that the reporting of adverse reactions to medicines should invariably be based on the specific preparation and not merely its active ingredient. As was clear from the earlier discussion, any substantial changes in formulation and more especially changes between fundamentally different drug delivery systems (e.g. the change from a tablet to an aerosol preparation) may have a very significant influence on the potential toxicity of the same dose of active chemical substance. The exclusive use of generic names in prescribing would also tend to undermine the economic

foundations on which recent pharmaceutical innovation and the establishment of new standards of pharmaceutical quality have been based. In this field, there is an important role for the pharmacist as well as the clinical pharmacologist. The changing pattern of trade mentioned at the start of this paper has largely eliminated the pharmacist's role as a skilled 'manufacturing' craftsman. However, the general discussion about the complexity of nomenclature for medicines and the importance of bioavailability as a concept underlines the need for better information for the prescriber. While clinical pharmacologists have an important part to play in the formal process of medical education on these matters, the practising pharmacists can provide a vital day-to-day information service for the doctors.²⁸ The pharmaceutical industry and the pharmaceutical profession should work closely together to make this service to the practice of medicine as valuable as possible. It is therefore encouraging that in Britain and many other countries there is already a sound understanding between the industry and the profession on the proper role of pharmaceutical brand names in prescribing. By contrast, the present lack of rapport in the United States on these matters is particularly unfortunate. There is also an important role for the pharmacist when patients are returned to the care of their general practitioner after having been receiving medicines as an outpatient or inpatient in hospital. It can cause serious confusion and distress if the patient sees that the physical appearance of his medicament has changed as a result of its being prescribed by his general practitioner instead of the hospital. It is therefore important that continuity should if possible be maintained, with the same medicine (and not just the same active ingredient) being prescribed for the patient both inside and outside hospital. If there is a change because different brands (or generic preparations) have been dispensed, the pharmacist must be prepared to look into the matter and take steps to reassure the

²⁷ The criticism of the use of brand names by clinical pharmacologists may to some extent have arisen from a confusion between pharmacology itself and the more recently evolved specialty of clinical pharmacology. The former is concerned exclusively with the various actions of the drug or pharmaceutical chemical entity in both animals and man. The latter, by contrast, should be concerned with the action of the specific medicine (not just the chemical) in an individual patient or group of patients; hence clinical pharmacology is concerned with the formulation as well as the active ingredient. The 'generic' chemical name is obviously relevant for the former; the pharmanespecific name is relevant for the latter.

²⁸ The recent emergence of a new specialty of 'clinical pharmacy' clearly recognises this fact.

patient, or if necessary advise the new prescriber of the position.

More than anything, however, there needs to be a reconciliation between the practical and scientific benefits of using brand (or pharma-specific) names in prescribing on the one hand, and some clinical pharmacologists' preference for the use of non-proprietary (drug) names in their teaching on the other. Prescribers, dispensing pharmacists and medical teachers all need to recognise that each type of name has its own part to play. The quality of care under the National Health Service would be significantly enhanced – at little if any monetary cost – if brand names and non-proprietary names were each used in their appropriate context in teaching. This would encourage prescribers more readily to link the two in their minds at the moment when they select a specific medication for their patient. It would also confirm their intuitive realisation that there is often much more to a specific medicine than merely the active chemical ingredient from which it has been formulated.

