

*'Innovative Chemical Extensions'*  
*the economic basis of*  
*pharmaceutical progress*

The ninth in a series of  
Office of Health Economics monographs  
dealing with aspects of the  
prescription medicine market

Nicholas Wells

With a foreword by  
Lord Butterfield

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The Office of Health Economics was founded in 1962 by the Association of the British Pharmaceutical Industry. Its terms of reference are:

To undertake research on the economic aspects of medical care.

To investigate other health and social problems.

To collect data from other countries.

To publish results, data and conclusions relevant to the above.

The Office of Health Economics welcomes financial support and discussions on research problems with any persons or bodies interested in its work.

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## Foreword

This is an important paper based on original economic analyses of the new entrants to various pharmaceutical sub-markets. To use a sporting analogy, it indicates that the first one away from the starting line, or even the leader after the first lap, will not necessarily be the eventual winner of the race. Quite late entries in particular pharmacological sub-groups may turn out to be the most valuable and the most widely prescribed of all the alternatives eventually available. These findings are strong arguments against the introduction of so-called 'need clauses' in decisions to licence or reimburse a new medicine. And the true value of what are often disparagingly described as 'me-too' medicines may not be established until several years after they have been available for prescription. It is simply not possible to predict how necessary a medicine will prove to be before it has been marketed.

For this reason, Nicholas Wells' other main contribution in this paper has been to coin a new phrase – 'innovative chemical extensions', or 'ICEs' – for the chemical variants which are developed after a major novel innovation. It is a usefully descriptive phrase indicating the idea of an innovative advance building upon established therapies whilst avoiding altogether the inaccurate notion of direct duplication implied by the term 'me-too'. Apart from their own therapeutic importance, Wells' paper demonstrates that 'ICE's are essential for the economic support of pharmaceutical innovation as a whole. They make

important contributions to the welfare of patients, not only through their own direct role in therapy but also through their contribution to the forward progress of medicine as a whole. I believe the process of pharmaceutical innovation would be very seriously hindered by any attempt to limit it to major 'breakthrough' innovations alone. That would seriously restrict the future benefits for patients, which, after all, is what pharmaceutical innovation must always have as its main objective. I hope this paper helps readers to understand the role of 'ICE's in this connection: we all owe Nicholas Wells our gratitude for his analyses and what they have demonstrated.

So I am very pleased to commend this latest OHE publication to you. It traces the author's analytical thought about the process of successful developments of improved new medicines. It shows that, from the innovative new chemical entities created by the pharmaceutical industry there emerge not just the ill-fated compounds, the so called 'me-too's', but much more significantly, the 'winners' – anyway until they too are overtaken in their post-marketing phase by even better compounds. This is the evolutionary aspect of the pharmaceutical revolution. I say pharmaceutical not simply pharmacological because this word embraces the whole outcome of all the complexities of treating the public for disease, world wide.

*John Butterfield*

## Acknowledgements

The author would like to express his gratitude to Robert Chew, statistician at OHE, for assistance in compiling the market data contained in this paper and to Amanda Williams of the Association of the British Pharmaceutical Industry for advice on the classification of the medicines embraced by the analysis.

**‘The most fruitful basis for the discovery of a new drug is to start with an old drug...’**

Sir James Black FRS, Nobel Laureate, Professor of Analytical Pharmacology, King's College Hospital Medical School, University of London, in a lecture entitled 'Precept and prejudice about managing R & D', reported in *Scrip* 18 May 1988. Sir James was instrumental in the discovery of two *novel* therapeutic agents, the beta blocker propranolol and the H<sub>2</sub> antagonist cimetidine.



Medicines have become a central element of health care provision. In the United Kingdom in 1986, the expenditure by the National Health Service (NHS) on pharmaceuticals, as represented by the net ingredient cost (NIC) of the medicines purchased, amounted to £2,171 million. This sum was equivalent to 11 per cent of the total cost of the NHS in that year. The largest part of annual NHS spending on medicines results from prescriptions written by general practitioners and dispensed by chemist and appliance contractors. In 1986, 77.2 per cent of the NIC medicines bill originated from this source,<sup>1</sup> meeting the cost of 397.4 million prescriptions. In recent years expenditure on pharmaceuticals in the primary care sector has risen at a slightly faster pace than that experienced by the NHS as a whole. Between 1980 and 1986 the total net ingredient cost of prescriptions issued by general practitioners and dispensed by chemists increased almost two-fold in unadjusted cost terms from £887 million to £1,676 million. Over the same period, the cost of the NHS increased from £11,911 million to £19,801 million. Consequently, the share of medicines within the overall spend rose from 7.45 per cent to 8.46 per cent.

As the cost of the nation's medicines bill has risen, attention has increasingly become focused on questions about the value-for-money associated with the use of pharmaceuticals in treating ill-health. In part these concerns reflect the less obvious nature of the economic pay-off from contemporary medicines compared to the clear benefits generated by the pharmaceuticals of 30 years ago. It is undeniable that conspicuous returns taking the form of reduced premature mortality, substantial savings in the hospital sector and diminished sickness absence from work only relatively infrequently accompany the medicines in common use today. Instead, the benefits now more usually assume the form of improvements in the quality of life and, in the absence of offsetting financial savings, they are achieved only at a net increase in cost to the NHS.<sup>2</sup>

Concern at the nation's rising medicines bill has also resulted in much closer scrutiny being given to the nature of the output of pharmaceutical innovation. In particular, it has been suggested that many of the new chemical entities (NCEs) being launched onto the pharmaceutical market are only minor chemical variants of those medicines already available and that

they offer few, if any, additional advantages over existing therapies.

In addition, it is argued that these 'me-too' products, as they are frequently entitled, can generate unnecessary extra cost for the NHS when priced at higher levels than competitive alternatives already on the market. Further, it is claimed that the research and development expenditures incurred by these medicines may represent a misallocation of scarce resources as there are many disease entities for which therapy at the present time is either inadequate or lacking altogether.

The alternative view rejects both the notion that 'me-too' products are evidence of the drug companies' poverty of inspiration' (Wyke 1987) and the criticism that the development of these medicines is wasteful of resources. Instead it is countered that breadth of choice in any given therapeutic area is beneficial because of the well-documented variations in the response of different patients to the same medicines. In addition, observation of the dynamics of innovation indicates that pharmaceutical progress today more usually proceeds via a series of incremental developments on existing medicines and only relatively rarely through 'isolated' scientific discoveries leading to compounds of substantial therapeutic novelty. Indeed, it is the revenues generated by the 'step-wise' approach, building upon established therapies, that provide the foundations for both the major and more minor forms of contemporary pharmaceutical innovation.

The debate about so-called 'me-too' medicines is of course much more complex and wide-ranging than might be inferred from the points adumbrated above. However, for the purposes of discussion, the topic might be split into two principal elements: scientific factors and economic considerations. The former sub-division embraces the merits of 'me-too' medicines from the perspective of pharmacological advance as well as the therapeutic implications for patients and has frequently been the subject of analysis and review.

In contrast, the economic significance of these medicines within today's patterns of pharmaceutical innovation is less well understood. It is therefore the objective of the present paper to examine and clarify this role. From analyses of the market performances of two annual cohorts of NCEs launched in the UK in the mid-1970s and of a specific therapeutic grouping it will be shown that negative presumptions about a new medicine's worth founded upon its seemingly close chemical similarity to already existing products are frequently ill-supported by subsequent product life cycle data. At the same time, the findings of the analyses will illustrate, *inter alia*, the large degree to which pharmaceutical manufacturers' resources and hence their ability to finance further research and

<sup>1</sup> Hospital prescribed medicines accounted for 17.8 per cent of the total and dispensing doctors for the remaining 5 per cent.

<sup>2</sup> Spurred by these developments a growing part of health economics research in recent years has been directed at devising new techniques to represent such quality of life improvements in quantitative terms. It should therefore become increasingly feasible to demonstrate (as in past decades with less sophisticated methods) that pharmaceuticals represent an economically efficient usage of scarce health service resources (Drummond *et al* 1988).



development are dependent upon innovations which some commentators choose to classify as 'me-too' preparations.

Throughout the paper, which first establishes the context for the discussion by outlining the nature of the pharmaceutical market and the competitive forces underpinning innovation, it will become increasingly evident that considerable doubt surrounds the validity of the term 'me-too' as it is applied to many of the new chemical entities entering clinical use today. 'Me-too' is clearly inappropriate when employed to describe a new medicine that has a related but nevertheless different chemical structure to that of existing pharmaceuticals since such dissimilarities can be associated with marked variations in pharmacological action. It is also seen to be a misleading and indeed patently inaccurate description when clinical preferences for individual medicines, initially crudely grouped together as 'me-too' products, are examined from a long-term perspective. Anticipating the emergence of these points and the more complete discussion of the question of terminology in the conclusion, the expression 'innovative chemical extension' (ICE) will therefore be employed throughout the paper to refer to those medicines that hitherto have been pejoratively and inaccurately described as 'me-too' preparations.

The range of medicines upon which the contemporary physician can draw is extensive but some degree of confusion surrounds the precise number of therapeutic substances that is currently available. This situation arises because medicines can be counted in several different ways (that is, a variety of definitions can be employed) and the necessary information can be drawn from a number of independent sources. The Drug Master Index (DMI), for example, listed 17,000 'medicines' as being available on the British market in 1983. However, the figure included preparations such as antiseptics, disinfectants, dressings, appliances and 5,000 homoeopathic dilutions. If these items are excluded the total falls to approximately 9,300 orthodox medicines. Further reduction is possible by also omitting those products classified as general sale items. This process leaves a total of between 5,500 and 6,000 prescribable formulations in the mid-1980s (Snell and Griffin, 1984).

Approaching the task of enumeration from the opposite direction, Walker and his colleagues (1985) counted 1,107 active ingredients listed in the Monthly Index of Medical Specialities (MIMS). This chemical base gave rise to 1,507 discrete single and combination products. Taking account of different routes of administration and formulations further increased this figure to an estimated 3,900 branded medicines that were prescribable by doctors in the UK in the mid-1980s.

Inconsistencies can therefore occur between the findings of independently conducted surveys to determine the number of medicines in use today. The differences principally reflect variations in selection criteria regarding routes of administration and formulations as well as discrepancies in the inclusion or exclusion of generics. Further variables that will influence the outcome of such counts and are likely to be of growing interest in the future include the legal category of the product (that is, whether or not it may be obtained without prescription) and its availability or otherwise at NHS expense. In reality, however, precise numbers are not strictly necessary from the point of view of the present discussion since the economic significance of the pharmaceutical market is effectively limited to only a relatively small number of products. The Informal Working Group on Effective Prescribing – the Greenfield Committee (DHSS 1983) – noted in its report that 'the average prescriber is said to use a range of 200–300 drugs'. This estimate suggests therefore that the market is dominated by, at most, 10 per cent of the products that are available for prescription.

Widening the analysis to take financial values into account confirms the level of market concentration implied above. Data gathered by Intercontinental Medical Statistics (IMS), the market research agency,



show that the top 300 medicines by value of sales to the NHS accounted for 82 per cent of the UK market<sup>3</sup> in 1985. This proportion falls only slightly to 74 per cent for the leading 200 products and to 60 per cent for the top 100. Further analysis indicates that the most valuable 50 products (in terms of revenue-generation) collectively gained 46 per cent of the market in 1985 whilst the top 10 most financially successful medicines together achieved a share of 21 per cent.

Putting these findings in perspective presents some difficulty because of the uncertainty that surrounds the true number of medicines available for use. The IMS data are based on the leading 600 branded and unbranded medicines prescribed by general practitioners and it is not clear exactly how many other products are located in the remaining segment of the market distribution. However, both MIMS and the British National Formulary are in broad agreement that there are currently about 2,200 branded medicines available to the prescribing doctor. If this figure is increased, albeit arbitrarily, to 3,000 in order to include unbranded generic products, then it can be estimated that 50 per cent of NHS expenditure on pharmaceuticals prescribed by general practitioners goes on only two per cent of available products and that 75 per cent is spent on just 6.8 per cent of the product total. Viewed another way, the distribution of product revenues in the pharmaceutical market is so greatly skewed that fewer than one medicine in every five achieves an annual turnover that exceeds the average value for all products on the market.

An even higher degree of market concentration than that revealed by an examination of the pharmaceutical market as a whole becomes apparent when the analysis is focused at the level of the submarket. Medicines compete within one or more of a large number of therapeutic classes and it is possible for a submarket to be dominated by a single product commanding a substantial share of the market's financial value. Within yet finer (and more appropriate) divisions of these therapeutic submarkets the share held by the leading product may be even greater. For example, data collected by Intercontinental Medical Statistics show that the top selling medicine within the category of cardiovascular preparations accounted for almost 11 per cent of this particular submarket's value in 1984 (Table 1). More specifically, the medicine concerned was a beta blocker and within this second level grouping it had a 41 per cent share of the market in that year. The corresponding situation for a selection of other therapeutic classes is also shown in Table 1.

**Table 1 Pharmaceutical market shares: sales of the leading product in selected therapeutic areas in 1984 expressed as a percentage of the values of (i) the total market (ii) the relevant sub-markets**

Therapeutic area (sub-market level 1)	Sales of leading product in level 1 sub-market as a percentage of value of:		
	Total mkt: per cent	Sub-mkt: level 1 per cent	Sub-mkt: level 2 per cent
1 Alimentary tract and metabolism	2.18	15.0	49.07
2 Cardiovascular system	2.26	10.68	40.83
3 Systemic anti-infectives	2.30	27.11	70.11
4 Musculoskeletal system	1.70	14.29	16.48
5 Psycholeptics	0.73	5.50	15.35
6 Respiratory system	2.37	20.43	33.06

Note: The identities of the level 2 sub-markets are as follows: 1 anti-peptic ulcerants; 2 plain beta blocker agents; 3 broad spectrum penicillins; 4 non-steroidal anti-rheumatics; 5 non-narcotic analgesics and anti-pyretics; 6 bronchodilators and other anti-asthmatics.

Source: Based on IMS data

It is therefore possible for one product to dominate a therapeutic submarket and this achievement in turn may underpin the commercial success of the manufacturer concerned. Table 2 illustrates this point with data relating to the leading eight companies (ranked by sales values) operating in the Family Practitioner Services sector of the NHS pharmaceutical market in 1986. Medicines with a 50 per cent or greater share of a submarket are shown frequently to account for an even higher percentage of the manufacturing companies' total sales. Thus company B's most important product in 1986 had a 56 per cent submarket share and contributed 73 per cent of total sales. However, there are, of course, exceptions to this observation. For example, company D's second ranking medicine gained 65 per cent of the financial value of the therapeutic grouping in which it was marketed in 1986 yet it generated less than 10 per cent of the company's overall sales revenues. In addition, the data for the main products of companies E and G indicate that it is possible for a medicine to achieve only a relatively modest share of a particular submarket whilst at the same time being of critical importance to an individual manufacturer's economic well-being.

In isolation, market share data therefore provide only limited insights into the commercial significance of any given product. Additional information about, *inter alia*, the importance of the submarket in which

<sup>3</sup> The market in this context comprises the medicines prescribed by general practitioners and dispensed by community pharmacists. By value, these sales account for nearly 80 per cent of NHS expenditure on pharmaceuticals measured at net ingredient cost.



the product competes and the latter's standing in relation to the company's other products is also required in order to make such an assessment. Consequently, the most telling point to emerge from Table 2 is the extent to which even the largest pharmaceutical manufacturers are dependent on the sales revenues of just one product. Computing simple unweighted averages for the data contained in Table 2 reveals that the leading medicine for each of the eight companies was one among as many as 23 products marketed yet it accounted for 65 per cent of total company sales. The picture painted by the data is therefore simultaneously one of success and vulnerability and in both cases the key determining variable involved is innovation. New product development offers the opportunity to gain a substantial share of a therapeutic submarket but at the same time it furnishes the means whereby competitors are able to pose a continuous threat to the successful position established by the original innovator.

**Table 2 Top eight companies: Number of products, main products share of company sales and of sub-markets, 1986**

Company	Number of products		Percent of total company sales	Percent of sub-market
A	15	1	49	30
		2	22	14
		3	15	9
		others	14	
B	33	1	73	56
		2	8	36
		3	7	28
		others	12	
C	14	1	63	49
		2	23	41
		3	7	12
		others	7	
D	17	1	77	54
		2	9	65
		3	6	44
		others	8	
E	23	1	59	17
		2	16	9
		3	10	30
		others	15	
F	34	1	32	50
		2	18	79
		3	16	20
		others	34	
G	33	1	81	39
		2	9	13
		3	2	10
		others	8	
H	16	1	88	65
		2	7	9
		3	2	36
		others	3	

Source: Intercontinental Medical Statistics

**Table 3 Changes in market ranking in two therapeutic sub-markets, 1970-84**

Non steroidal anti-inflammatory agents				
Rank Position in:				
Product	1970	1975	1980	1984
A		3	3	1
B			4	2
C			6	3
D	1	1	1	4
E	2	2	2	5
F			12	6
G			5	7
H	4	8	10	8
I		4	7	9
J		7	8	10
K		5	11	11
L			9	12

Bronchodilators and other anti-asthmatics				
Rank Position in:				
Product	1970	1975	1980	1984
a	5	1	1	1
b	4	3	2	2
c		4	3	3
d			5	4
e	1	2	4	5
f	3	6	7	6
g	2	5	6	7

Source: Based on IMS data

The competitive impact of innovation may be illustrated by examining changes in the market position of products over time. Table 3 shows the dynamics of two second level submarkets<sup>4</sup> – non-steroidal anti-inflammatories and bronchodilators/other anti-asthmatics – over the period 1970-1984. Focusing on the first of these therapeutic groupings, the data indicate that only one of the products shown for 1980 retained the same position in 1984. The leading two medicines in 1980, both of which had been available for more than a decade, had dropped to fourth and fifth position respectively in 1984.

More specifically, the first placed medicine in 1980 was succeeded in 1984 by a product which had been introduced onto the market in 1973. In the process of transition the former suffered a reduction in annual sales of 12 per cent in conjunction with a loss of market share of 48 per cent. In losing second place in 1984 to a medicine introduced at the turn of the decade, the 1980 incumbent of this position experienced a 14 per cent fall in market share. In the bronchodilator/other anti-asthmatics therapeutic grouping, the data shown in Table 3 suggest that a critical wave of innovative change was

<sup>4</sup> The term second-level is used to identify a more specific therapeutic class within broad market categories. In this instance, the anti-inflammatories are a segment of the musculoskeletal preparations submarket whilst the anti-asthmatics are part of the respiratory medicines grouping.



experienced in the late 1960s and early 1970s. None of the market positions achieved by the available products in 1970 was retained in 1975. The second and third ranked products in 1970, for example, had by 1975 both lost two-thirds of their market shares. Conversely, a medicine that had been introduced onto the market in 1968 more than trebled its market share from 12 per cent to 39 per cent between 1970 and 1975, improving its market ranking from fifth to first position.

Innovative success in a specific therapeutic submarket may, if the latter is of sufficient magnitude, also be reflected in aggregated data for the pharmaceutical market as a whole. Table 4 shows the leading 10 medicines by sales values in 1980 and their subsequent market ranking in 1984. None of the products concerned succeeded in retaining the same market position over the four-year period. Indeed, seven out of the ten experienced a worsening of their market position and of these five dropped out of the top ten altogether. Table 4 also shows the 1980 position of those products occupying the leading ten market rankings in 1984. These data reveal that half of the latter year's top ten places were held by products that had not been so positioned in 1980. In one case, the medicine in question had not even been launched onto the market in 1980.

The ramifications of shifting product fortunes are to varying degrees mirrored in data illustrating company rankings over time. Table 5 shows the changes in the league table positions of the top 10 companies during the decade 1975–85. The degree of 'repositioning' over the period is not as great, however, as that seen at the product submarket level. This finding might have been anticipated since the large companies tend to have more extensive product portfolios than their smaller competitors which in turn means that a decline in the revenues generated

by one particular medicine might be counterbalanced by more successful market performances elsewhere in the product range. Nevertheless, the data do still show a number of quite marked alterations in market ranking, especially in the lower reaches of the top ten grouping. For example, the seventh placed company in 1985 had been positioned as low as thirty-third ten years earlier whilst another manufacturer improved from twenty-second to eighth place over the same period. In both instances, success was founded upon the introduction of a major new medicine to the pharmaceutical market.

Data showing market shares and product/company rankings inevitably provide only limited insights into the workings of the pharmaceutical market. In particular, such information fails to shed light on many of the factors that underpin the development of specific therapeutic submarkets over time. For example, demographic change and related shifts in the incidence and prevalence of certain diseases as well as alterations in diagnostic and therapeutic fashions are clearly relevant influences that remain hidden by the data presented in their most basic form. The impact of product innovation is, however, more clearly discerned. New medicines may simply be improvements upon, or offer wider therapeutic possibilities than, established treatments or, more radically, they may offer entirely novel approaches to disease management (as in the case of the introduction of H<sub>2</sub> antagonists for peptic ulceration). In both instances, the implications for the commercial well-being of the innovating company and, indeed, its competitors are potentially far-reaching. It is not surprising, therefore, that pharmaceutical manufacturers invest a considerable proportion of their resources in the search for, and development of, new medicines.

**Table 4** Market ranking of 1980's leading 10 products in 1984 (column A) and the position of 1984's top 10 in 1980 (column B)

A		B	
1980	1984	1980	1984
1	4	2	1
2	1	5	2
3	16	8	3
4	10	1	4
5	2	–	5
6	14	32	6
7	21	12	7
8	3	15	8
9	11	25	9
10	18	4	10

Source: Based on IMS data

**Table 5** Ranking of 1975's leading 10 pharmaceutical companies (by sales values) in 1985 (column A) and of 1985's top 10 in 1975 (column B)

A		B	
1975	1985	1975	1985
1	1	1	1
2	4	8	2
3	3	3	3
4	5	2	4
5	6	4	5
6	10	5	6
7	8	33	7
8	2	22	8
9	20	7	9
10	12	18	10

Source: Based on IMS data



# Innovation and 'innovative chemical extension' (ICE) medicines

It is estimated by the Association of the British Pharmaceutical Industry (ABPI 1988) that pharmaceutical manufacturers in the United Kingdom spent £668 million, or 13.7 per cent of the value of gross output, on research and development in 1987. This sum, which includes revenue and capital spending on investigations into prescription, proprietary and veterinary medicines, has risen substantially in recent years. In 1980, for example, research and development expenditure was equivalent to only about one third of the current sum. Even after the impact of inflation has been taken into account, the increase in spending over the seven-year period still exceeded 80 per cent in real terms. The explanation for this magnitude of increase lies in the rapidly escalating costs of developing a new medicine. Precise figures for the investments required to bring a candidate medicine from the laboratory to the market are difficult to compute but recent estimates suggest a contemporary cost of between £50 million and £100 million (Table 6).

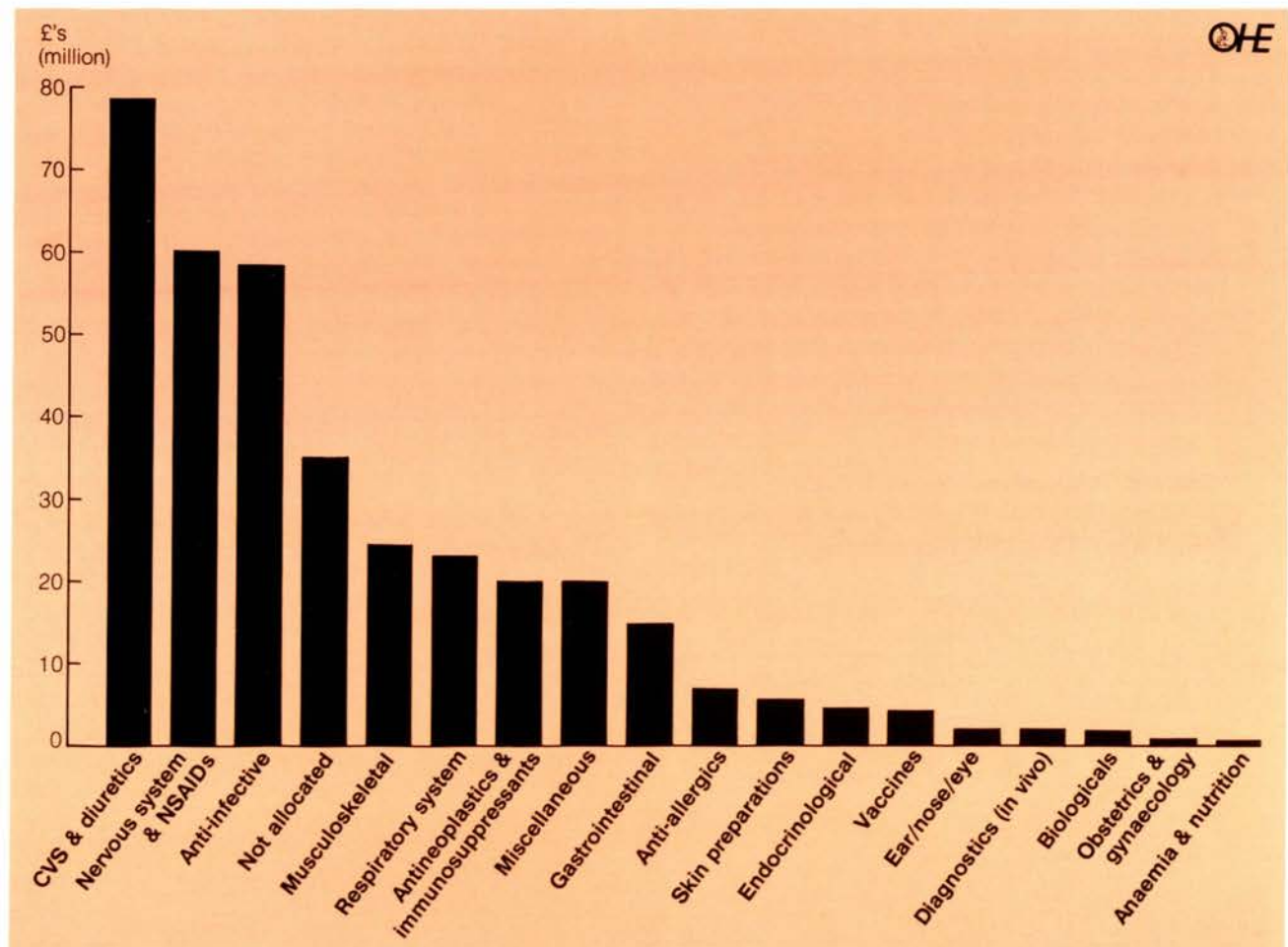
**Table 6** Estimates of the cost of researching and developing a new drug reported in selected surveys

Cost (million)	Year	Cost (£million 1986) (retail price index adjusted)
> £50	1986	> 50
\$35-91	1982	24-63
> \$70	1982	> 48
\$50-68	1976	69-93
\$54	1976	74
\$57.4	1985	46
SFr 182	1984	64

Source: Lumley *et al* 1987

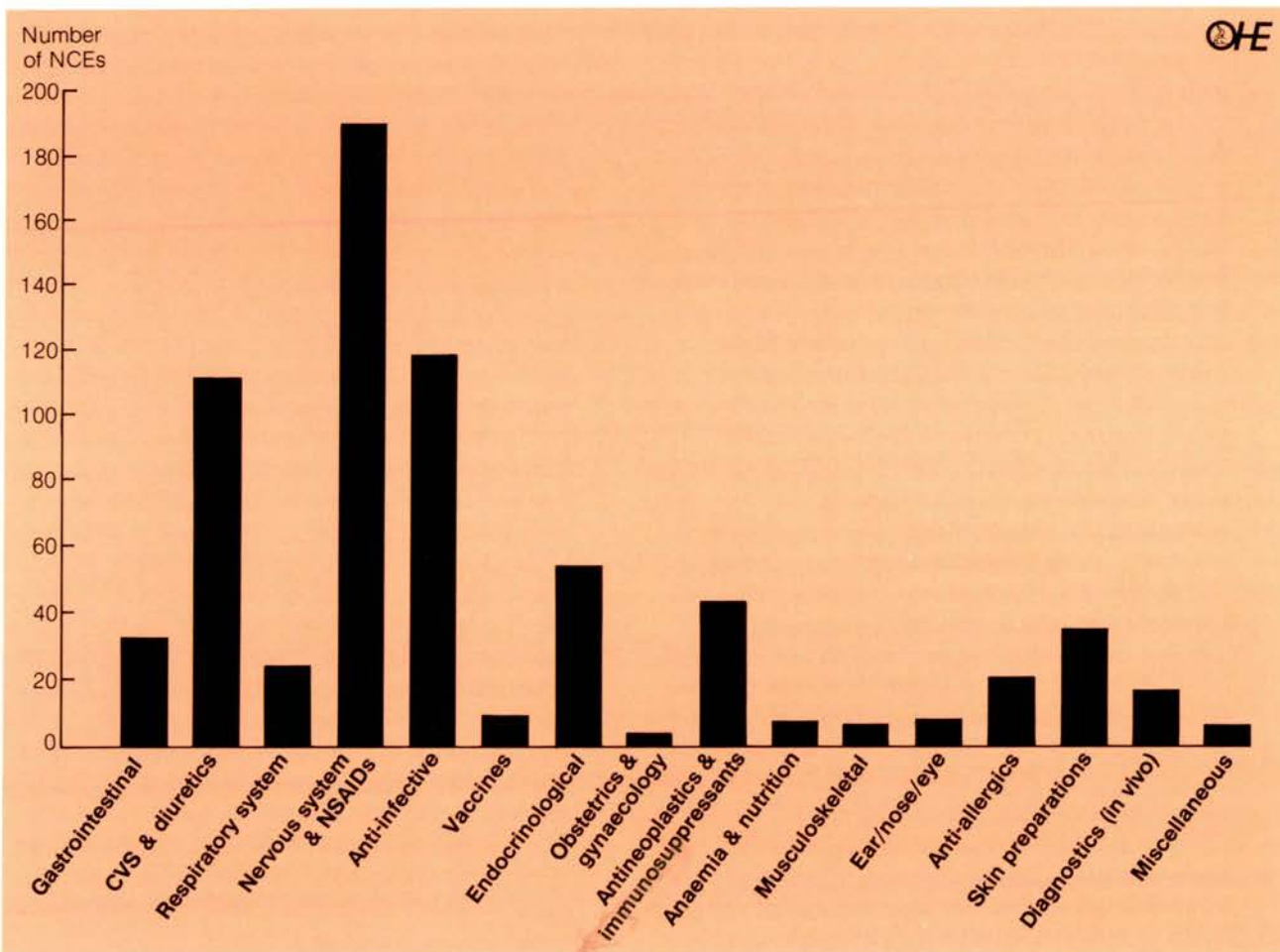
The research and development expenditure survey conducted by the Centre for Medicines Research (CMR) in 1986 indicated that revenue spending comprised 82 per cent of the UK industry's outlay on R&D whilst capital projects accounted for the

**Figure 1** Revenue R and D expenditure by therapeutic class in 1986



Source: Parrish *et al*, 1987

**Figure 2** Therapeutic classes of New Chemical Entities (NCEs) marketed in the UK (1960-1986)



Source: Centre for Medicines Research

remaining 18 per cent of the total (Parrish *et al* 1987). The survey also collected sufficiently detailed information to allow a breakdown of the revenue expenditure by therapeutic class. The findings indicated that just three targets of medicines research – preparations for the cardiovascular system, anti-infectives and agents acting on the central nervous system (including non-steroidal anti-inflammatories) – absorbed over half (54.4 per cent) of revenue research and development expenditure in 1986 (Figure 1). Furthermore, the results of previous CMR surveys show that the significance of this group has been increasing over time (Parrish *et al* 1987). In 1983, for example, the three therapeutic classes accounted for 45.7 per cent of the industry's revenue expenditure on research and development.

The innovative output flowing from the investment in research and development is usually measured in terms of the numbers of new chemical entities (NCEs) that become available for prescription use. It is not possible, however, to identify and assess quantitatively the relationship between resource

input and product output, especially when the analysis is being conducted at the level of the industry as a whole rather than on an individual company basis. The explanation for this situation lies quite simply in the absence of appropriate information. Figures for the industry's expenditure on research and development in any one year do not relate to a cohort of completed products but to numerous candidate medicines which are individually at very widely differing stages of development. On the output side of the equation, available data show the number of new chemical entities launched annually onto the UK pharmaceutical market although only a fraction of these introductions will have resulted from research and development work conducted entirely or principally in this country. The two sets of global data are therefore mismatched and cannot be combined to derive an input-output relationship for the UK industry's research activities. Nevertheless, information published by the CMR showing the cumulative total of NCEs launched in the UK between 1960–86 (Figure 2) reflects the pattern of research expenditures outlined above with cardiovascular,



anti-infective and central nervous system preparations accounting for more than 60 per cent of the 669 medicines introduced onto the market over the period.

It is not surprising that these three therapeutic classes attract a significant proportion of the research and development resources deployed by the pharmaceutical industry. The diseases in which the medicines are used to prevent, alleviate or cure symptomatic illness – for example, stroke, coronary heart disease, arthritis and bacterial infections – are some of the most prevalent, handicapping and economically burdensome experienced by contemporary society. Substantial volumes of research funds are further committed to these areas of investigation because of the considerable potential that clearly exists for the development of novel and more effective means of therapeutic intervention with pharmaceuticals. Within the circulatory disorders, for example, current research suggests that relatively recent innovations in the treatment of hypertension such as calcium antagonists and angiotensin converting enzyme inhibitors could be followed by potassium channel activators, orally active renin inhibitors and atrial natriuretic factors (ABPI 1988a).

However, the concentration of such a large part of the pharmaceutical industry's research and development effort in the cardiovascular, central nervous system and anti-infective fields has also attracted criticism. One view is that the ordering of research priorities in this way reflects an attempt by manufacturers to reduce the scientific risks inherent in the innovative process. Limiting investigative activities to large therapeutic areas in which a substantial knowledge base has already been established might, theoretically at least, be associated with a smaller number of false starts and fewer projects having to be abandoned at more advanced stages of development than might arise in the exploration of therapeutic territories that are less well understood. This argument carries a certain degree of intuitive appeal although current scientific developments in the cardiovascular field, as briefly exemplified above, and elsewhere suggest that its validity is waning as the potential for innovative progress (and hence risk) accelerates even in these seemingly 'safer' areas of research.

A further frequently encountered criticism of the direction of the pharmaceutical industry's research and development spending is that the latter has resulted in an unnecessary proliferation of similar medicines in the therapeutic areas concerned. This phenomenon may, it is argued, have had three undesirable effects. First, it may have added confusion to the prescribing process. Distracted by the steady flow of new additions to their armamentarium, doctors may have been inhibited from becoming

more familiar with the benefits and costs in therapeutic use of the medicines already at their disposal. Second, it is claimed that there may have been an unwanted opportunity cost effect: the distribution of substantial research funds to certain therapeutic areas has necessarily meant 'underfunding' elsewhere, particularly in those 'difficult' diseases where little (if any) effective treatment is currently available and innovation is arguably needed most. Third, it has been suggested that because the new medicines in question tend to be priced at higher levels than existing products they may have added to the National Health Service's medicines' costs without generating benefits for patients that are greater than those already associated with present therapeutic alternatives.

These three criticisms embrace a large number of complex issues and to attempt to address them individually in any detail is beyond the scope of the present paper. The first point, for example, would require a comprehensive discussion of the many factors that influence therapeutic decision making and, specifically, how the products of innovative research are integrated into this process. Given that there are about 30,000 doctors in general practice in the UK, it is also clear that a plethora of different approaches to the prescribing of medicines would emerge from such an analysis.

The second, or 'opportunity cost', issue raised by critics of the ICE approach to innovation begs a number of key questions, not the least important of which relate to the uncertainties surrounding the economics and potential outcomes of investing research and development resources in particular therapeutic classes. Most obviously there is, of course, no guarantee that increasing funding levels in an apparently 'neglected' area will lead to the creation of effective new medicines. Indeed, from a global perspective, it is possible that patient welfare as a whole may be diminished if potential therapeutic improvements are delayed or forgone in 'established' areas because of reductions in research spending. The third criticism, that concerning the inflationary pressures inherent in ICE medicines, is not as straightforward as it might appear at first sight. The price of a new medicine is not crudely determined on the basis of simply adding a premium to existing price levels. Instead, it is a function of a combination of variables including the additional innovative value offered by the product, the implications it may have for other sectors of health care provision, the stage it has reached in its life cycle (and hence the amount of effective patent coverage remaining) and the contribution that the product is required to make to the manufacturer's research and development costs (OHE 1975; Reekie 1977). The significance of these and other factors may be expected to differ over time and



between therapeutic classes so that generalisation about the financial implications of innovation for the NHS are, at the least, open to the charge of distorting oversimplification. At the same time, the notion that new ICE medicines offer few, if any, extra therapeutic benefits (either to the relevant patient population as a whole or to particular sub-groups of that community) may simply reflect inadequate attempts to seek out such gains or the failure to employ, or indeed the lack of, suitable techniques of evaluation capable of capturing such information.

Accepting the complexities outlined above, the prime purpose of this paper is to demonstrate that ICEs are in fact a significant, indeed essential, part of the economic underpinning of pharmaceutical innovation. One approach to meeting this objective is to analyse the commercial performances of those products comprising a given year's cohort of new chemical entity introductions and to distinguish between them on the basis of whether or not they might be categorised as ICE medicines. In this way, it should theoretically be possible to indicate the extent to which the latter contribute to the revenues gained by the cohort as a whole at different points in time after the year of market launch. Contemporaneously, the significance of these medicines to their manufacturers' financial position can be demonstrated by a simple extension of the analysis. In both instances, the choice of revenue figures as indicators of product performance reflects the availability of these data, the absence of arguably more appropriate information and, fundamentally, the fact that market success is the ultimate determinant of the ability and capacity to invest in research and development.

**Table 7 Market performance of NCEs first launched onto the UK pharmaceutical market in 1975 and 1976**

<b>1975</b>	
Number of NCE launches identified by CMR	20
Number of NCEs remaining after exclusions (see text)	11
Total sales of 1975 cohort in 1980	£15.202m
– percentage attributable to ICEs	89%
Total sales of 1975 cohort in 1985	£21.827m
– percentage attributable to ICEs	90%
<b>1976</b>	
Number of NCE launches identified by CMR	18
Number of NCEs remaining after exclusions (see text)	7
Total sales of 1976 cohort in 1981	£49.864m
– percentage attributable to ICEs	44%
Total sales of 1976 cohort in 1986	£98.407m
– percentage attributable to ICEs	53%

Source: Based on CMR and IMS data

### Cohort analysis

Table 7 contains the results of applying the methodological approach described above to the cohorts of new chemical entities which were introduced onto the UK market for the first time in 1975 and 1976. The products themselves were identified from the data base constructed by the Centre for Medicines Research whilst the market values they achieved over the subsequent decade were obtained from the audits carried out by Intercontinental Medical Statistics. It should be noted that the latter data are concerned only with medicines prescribed in general practice. Consequently, those new chemical entities employed exclusively in hospitals have been omitted from the analysis. Other NCEs contained in the original cohorts were also eliminated from the exercise if annual sales revenues 10 years after launched had failed to attain a threshold level of £250,000<sup>5</sup> (either because of inadequate demand or market withdrawal).

One of the most notable findings shown in Table 7 is the considerable difference that exists in the aggregate sales performance of the two groups of NCEs over the subsequent 10-year period. The gap is all the more striking when account is taken of the differing number of 'remaining NCEs' originating in the two years: the average tenth year sales per product for the 1976 cohort was seven times the corresponding figure for the group of new medicines launched in the preceding year.<sup>6</sup>

However, from the specific viewpoint of this paper, the importance of the findings shown in Table 7 lies in their confirmation of the central role played by ICE medicines in pharmaceutical innovation. About 90 per cent of the collective revenue achieved by the 1975 cohort in both 1980 and 1985 was attributable to medicines that might be categorised as ICE products. For the medicines launched onto the UK market for the first time in 1976 the corresponding proportion averaged out at around 50 per cent. Since pharmaceutical manufacturers finance research and development initiatives out of current revenue, these findings suggest that attempts to restrict the market access of ICE medicines could significantly jeopardise the prospects for innovative advance (in addition, most obviously, to curtailing the immediate supply of new products to the prescribing physician). The former point is yet more forcefully made when the perspective of the analysis is switched to that of the individual manufacturer. Taking first the 1975

<sup>5</sup> At or below this level of sales, the products concerned would not have been captured by the IMS audit of the leading 600 medicines on the UK pharmaceutical market. In 1986, sales of the 600th placed product exceeded £300,000.

<sup>6</sup> More detailed analysis (not shown in Table 7) reveals that much of the 'success' of the 1976 NCE group in fact revolved around just two products – together they accounted for over 80 per cent of the revenue gained by the cohort as a whole in 1986.



**Table 8** Contribution of individual products within the 1975 and 1976 NCE cohorts to manufacturers' revenues 10 years after market launch

a) 1975 Cohort			
ICE		Novel	
Product	Per cent of company's revenue in 1985	Product	Per cent of company's revenue in 1985
A	11.6	J	100.0
B	2.1	K	1.5
C	1.4	L	19.9
D	22.8		
E	4.9		
F	23.7		
G	13.1		
H	14.3		
I	2.0		

b) 1976 Cohort			
ICE		Novel	
Product	Per cent of company's revenue in 1986	Product	Per cent of company's revenue in 1986
a	62.7	e	79.7
b	74.7	f	18.3
c	0.9	g	2.1
d	56.5		

Source: Based on CMR and IMS data

cohort of NCE introductions, the analysis contained in Table 7 identified 20 new chemical entities of which 12 were retained for further analysis.<sup>7</sup> Table 8a shows the commercial significance of the latter medicines for their manufacturers. Of the 12 products, nine were classified as ICEs and within this group more than half (5) were responsible for at least 10 per cent of their originators' revenue in 1985. In two cases, the medicines concerned contributed nearly a quarter of their respective companies' income from the UK market in that year. At the other extreme, however, four of the nine ICEs generated less than five per cent of their manufacturers' UK earnings in 1985. Disparities on an even greater scale are apparent when the analysis is repeated for the 1976 cohort of NCEs. Ten years after market launch, three of the four ICE medicines shown in Table 8b had become major contributors to the overall revenue performance of their manufacturers. Product b, for example, accounted for 75 per cent of its originator's sales in 1986. At the other extreme, product c was generating only one per cent of the 1986 revenue of the company which had first placed it on the market 10 years earlier.

7 For this part of the analysis, one of the NCEs belonging to the 1975 cohort is treated as two separate products since the chemical entity was marketed under two different brand names by two separate manufacturers. Consequently, the total of 11 'remaining' NCEs shown in Table 7 becomes 12 in Table 8.

**Table 9** Leading 10 pharmaceutical companies in 1986: percentage of revenue derived from first and second ranked medicines, identified as either novel or ICE products

Percentage of company revenue attributable to leading products:		
Company	Product no 1	Product no 2
A	<b>49</b>	22
B	73	8
C	63	23
D	<b>77</b>	15
E	<b>32</b>	19
F	<b>80</b>	8
G	70	20
H	89	7
I	29	16
J	45	33

Note: Figures in bold signify a novel compound and those in italics indicate an innovative chemical extension

Source: Based on IMS data

A similarly variable pattern emerges from an examination of the income base of today's leading manufacturers. Table 9 shows the top ten pharmaceutical companies (by sales value) operating on the UK market in 1986 and, in each case, the percentage of annual revenue contributed by the leading two products. The latter are categorised as either novel compounds (bold type in the table) or innovative chemical extensions (italics). Only one of the leading 10 companies is shown to have as its leading two revenue generators medicines that may be classified as core pharmaceutical innovations. Three other manufacturers have a novel medicine as the most valuable asset in their product portfolio and an ICE ranked in second position. However, for each of the remaining six companies, the two most important products in terms of revenue generation are of the ICE type, that is medicines launched onto the market sometime after the entry of the original core innovation into prescription use. The economic contribution of these products ranges widely – from seven per cent of sales revenue (company H's second ranked medicine) to 89 per cent (company H's first placed medicine). However, the key points established by the data in Table 9 are, first, that ICEs are numerically predominant among the medicines covered by the analysis (15 out of the 20 products) and second that this group of chemical entities is, collectively, responsible for a substantial proportion of the revenues earned by the leading research-based pharmaceutical manufacturers. Five of the 10 companies in Table 9 derived 75 per cent or more of their annual income on the UK prescription medicine market in 1986 from one or at most two products classified as ICEs. Overall, the 10 companies



secured 34 per cent of the value of the pharmaceutical market in 1986 and within this total 51 per cent stemmed from ICE medicines ranked either first or second in their manufacturers' product portfolios. The foregoing has sought to show that ICE medicines play a key role in financing pharmaceutical innovation. Of course, a number of cautionary points must be stressed about this type of analytical approach. It is, for example, obviously necessary to be wary of generalisation in this field since individual ICEs can clearly make substantially different contributions to their innovators' revenues.<sup>8</sup>

Furthermore, considerable interproduct variation is likely to exist with regard to the distribution of these income streams over the life cycles of the medicines concerned. It is also axiomatic that the simple percentage data contained in the analyses above convey nothing about the magnitude of the revenue produced by ICE and other medicines. A chemical entity responsible for 'only' 10 per cent of a company's revenue may in fact be yielding a considerably greater absolute volume of resources for potential investment in research and development than one accounting for, say, 50 per cent of another manufacturer's total sales. Finally it should be emphasised that pharmaceutical companies market their products internationally and it would not be appropriate to assume that the relative significance of a given medicine in one particular market accurately reflects its overall standing within the product portfolio of the company when the latter's global trading operations are taken into account.

Nevertheless, none of the points highlighted above invalidates the basic hypothesis that ICE medicines comprise a fundamental component of the process of pharmaceutical innovation. Perhaps the major weakness of the analysis therefore lies in the problem of defining an ICE medicine. New chemical entities often do not divide neatly into those medicines that can clearly be categorised as ICEs and those that are truly novel innovations. In what may be regarded as borderline cases, allocation to one or other category may, in the final analysis, involve an element of subjective assessment that cannot of course be guaranteed to command universal agreement. Difficulties of a related nature would similarly undermine more sophisticated analyses attempting to differentiate between ICE products themselves. Clearly some medicines characterised under this general term offer greater degrees of chemical novelty, therapeutic benefit or fewer unwanted side effects than others.

Against this background, the calculations presented earlier do not pretend to high levels of precision. Nevertheless, it remains clear that an important element of research and development funding depends upon the revenue generated by ICE

medicines and that attempts to restrict their access to the market may significantly damage the prospects for innovation. At best this might mean a loss of innovative productivity directly in proportion to the reduction in available research funds. At worst, it is conceivable that the latter could be pushed down below a threshold level at which investment in innovation ceases to be a viable option for some pharmaceutical manufacturers.

### Sub-market analysis

The significance of ICE medicines in pharmaceutical innovation can also be illustrated by examining the evolution of individual therapeutic sub-markets. For this paper the medicines commonly referred to as the beta blockers, which are used in the management of raised blood pressure and angina, have been selected for analysis. The choice reflects the fact that innovations within this group of products have, in common with new introductions in the therapeutic categories of minor tranquillisers and non-steroidal anti-inflammatories, frequently been criticised as unnecessary duplications of existing medicines. At the same time, beta blockers are a relatively important item of expenditure for the NHS. Although only nine million prescriptions for these medicines were dispensed by chemists in Britain in 1986 (2.3 per cent of the total), they accounted for £1 in every £18 of the net ingredient cost medicines bill.

The starting point for the analysis was the identification of single beta blocker medicines (that is, the study excluded combinations of these agents with other therapeutic substances) achieving sufficient sales revenues to be included in the IMS leading 600 products<sup>9</sup> each year between 1970 and 1986. The sub-market has expanded considerably over the 16-year period. In 1970 there were only two beta blockers on the market. By 1986 the number of discrete single entities had risen to 10 and the financial value of the market (including innovations launched in parallel as well as later introductions of branded and straight generics and long-acting formulations) had increased by 60 times.

The mid-1970s were a particularly innovative period for this group of medicines. Between 1974 and 1976, six beta blockers (involving eight different brands) were launched onto the market. Indeed between the

<sup>8</sup> In this particular context it should also be noted that the preceding analysis of the contribution of individual ICE medicines to their originators' annual revenues has been undertaken at the level of the company rather than the corporation. Had it been conducted at the latter level, the relative revenue contribution of individual medicines would obviously have been smaller in those cases where several companies belonged to the same corporate parent.

<sup>9</sup> Between 1970 and 1974, the IMS audit covered only the leading 400 products, although this group still accounted for 88 per cent of the market. (The leading 600 in recent years have summed to about 93 per cent of total sales.)



end of this period and 1986 only two further new preparations were granted licences for sale by the regulatory authorities (in 1977 and 1979) so that for virtually all of the products in this sub-market there has been at least a decade of use in clinical practice. And this latter experience has of course been one of the key elements in shaping the development of the beta blocker sub-market.<sup>10</sup>

It is clear from the data in Table 10 that individually beta blocker medicines do not adhere to a common pattern of market performance. At one extreme, for example, the launch in 1970 of product C appeared to herald the arrival of a new chemical entity of major significance. Within two years it had become market leader, gaining 43 per cent of sales in the therapeutic category. In 1974, however, the medicine was found to have serious side effects that led rapidly to its withdrawal from the market.

The launch in 1976 of Product K represents an example from the opposite end of the spectrum of market experience. This medicine first became

available for use at a time when there were already seven discrete beta blocker agents established on the market and, in contrast to the performance of product C described above, within two years it had only gained a 13 per cent share of the market's value. The medicine's subsequent use in clinical practice has, however, shown it to possess advantages over competitor products and in 1986 it was the most frequently prescribed single beta blocker in the primary care setting, capturing a market share of 49 per cent.

Between these extremes of market fortune lies, of course, a series of more or less successful performances. Some beta blockers entered the market and rapidly achieved a level of sales that fluctuated little over time. Other products have demonstrated a classic pattern of 'growth and decay' with their market value increasing steadily for a few years after launch only to be followed by an equally steady decline in financial return.

There exists, therefore, considerable variation in the patterns of commercial success achieved by individual beta blocker medicines but common to all of these products is the fact that market performance at the time of launch is highly unpredictable.

In the context of such an innovatively competitive market as pharmaceuticals this observation may perhaps appear to be an unnecessary statement of the obvious. However, its relevance from the viewpoint of the present paper is that it is precisely this element of uncertainty that serves to undermine the 'me-too' type of criticism levelled at the process of pharmaceutical innovation. Much critical comment appears to be founded upon the notion that the significance of specific new chemical entities is clearly understood at or before market launch and that one of the key indicators in this regard is the innovation's chemical composition in relation to the

<sup>10</sup> Other factors also play an important role in this evolutionary process. For example, promotional strategies and company/brand reputation and the loyalty the latter attracts play some role in influencing market shares. At the same time, therapeutic sub-markets are subject to 'external' influences upon their long-term development, including demographic trends, alterations in the incidence and prevalence of illness, changes in approach to disease management (and prevention) and shifts in therapeutic fashion. Focusing on the last mentioned, beta blockers are employed principally in the control of angina and raised blood pressure and the widening of therapeutic options in either or both of these diagnostic areas – as has occurred in hypertension, for example, with the advent of calcium antagonists and ACE inhibitors – will obviously have an impact on the shaping of this pharmaceutical sub-market. Nevertheless, once the market boundaries have been established, it is clinical experience and the therapeutic preferences thereby generated that remain the key determinants of a sub-market's profile. In the specific context of the beta blockers it will therefore be instructive to monitor the reaction of prescribers to the new 'wave' of preparations – such as carvedilol, dilevalol and celiprolol (*Scrip* 1988) – and to assess the extent to which these innovations eventually reorder the market patterns observed at the present time.

**Table 10** Market share gained by medicines in the beta blockers therapeutic sub-market, percentages

Medicine	Year of Introduction	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986
A	1965	88	48	34	27	23	33	39	34	31	28	24	23	22	20	18	14	12
B	1970		15	18	26	37	50	48	45	40	36	31	26	23	20	17	14	12
C	1970	6.6	32	43	42	35	8.1											
D	1974						1	0.9	0.7	0.5	0.6	0.6	0.6	0.7	0.9	0.9	1	1
E	1974						1.7	1.6	1.2	1	0.7	0.8	0.6	0.5	0.5			
F	1974						0.6	0.6	0.7	0.5	0.5	0.4	0.4	0.7	0.8	0.8	0.8	0.6
G	1974						1.7	1.8	1.4	1.5	1.1	0.9	0.8	0.7	0.6	0.7	0.7	0.6
H	1975							1	1.6	1.9	3.1	3.9	4.6	5.1	5.4	5.4	5	4.6
I	1975						0.7	1.9	2.3	2.6	3.2	3.2	3.1	3	2.9	2.8	2.6	2.4
J	1975						2.3	4	3.7	4.6	5.2	5.3	5.9	5.4	5	4.6	4.1	3.8
K	1976							1.4	8.5	13	17	20	23	28	33	41	48	49
L	1977								1.5	3	3	4.4	5.3	5.8	5.7	5.2	5.1	5.1
M	1979										0.6	1.2	1.8	2.2	2	1.7	1.7	1.4



**Table 11** Beta-adrenergic blocking agents and their differing properties and clinical indications

<i>Drug</i>	<i>Properties</i>	<i>Indications</i>
Practolol	Oculo mucocutaneous	Cardiac arrhythmias only
Propranolol	The most widely investigated	All suitable uses
Labetalol	Additional alpha-receptor blocking activity	Causes less bradycardia and less coldness of the extremities
Oxprenolol Pindolol Acebutolol	Intrinsic sympathomimetic activity	
Atenolol Nadolol Sotalol	Water soluble	
Metoprolol Atenolol Acebutolol	Cardioselective	Lower effect on bronchial airways

Source: Snell, 1988

corresponding structural characteristics of those products already available in the therapeutic category. In reality, however, medicines of an apparently similar chemical construction may possess significantly different pharmacological, toxicological and other properties and the benefits/disadvantages they confer may only fully emerge during the course of extensive clinical usage.

It therefore follows from this argument that attempts to restrict the number of new chemical entities allowed onto a given sub-market may risk the loss of significant therapeutic advance. This point may be illustrated from the beta blocker market. If, for example, a limit of three had been placed on the permitted number of introductions to the market many valuable medicines now in use may not have become available. This observation applies to the product (K) that has now become firmly established as market leader. Combining IMS market value data and the price information contained in MIMS (one of the reference booklets available to GPs) it may be estimated that prescriptions for the medicine in 1986 amounted to more than 450,000 patient years of treatment. A further 200,000 treatment years involved another eight beta blockers (medicines D, F to J, L and M) that similarly would have been denied access to the market. The beta blockers available at the present time offer a range of therapeutic options (Table 11) and to a large extent these would have been forgone had physicians been forced to rely only on the first three medicines to reach the market. Such restriction of choice would clearly have had important implications for the quality of disease management and patient care.

At the same time, it is also evident that market size limitation in this way would fundamentally jeopardise the whole process of pharmaceutical innovation.

Product K, for example, would not have gained market access under the entry rules hypothesised above, yet it is now market leader and generated approximately two-thirds of its manufacturer's UK earnings in 1986. As research and development programmes are financed out of current revenues, the inability to market this particular product might have seriously eroded the standing of the company concerned and its parent corporation as leading innovators in the modern pharmaceutical industry. Furthermore, taking the beta blocker market as a whole, it may be estimated that only about one quarter of its current financial value stems from sales of the first three medicines to be launched in this specific area of therapy.

Table 12 emphasises that the potentially damaging effects on innovation of market interference of this type are obviously not confined to the therapeutic category of beta blocker agents. The table shows the leading medicine in each of the 10 largest (by value) sub-markets and indicates, in each case, whether or not the product was introduced at a time when at least three chemically related alternatives were already established on the market. The analysis reveals that five of the medicines which had become market leaders by 1984 would not have been permitted access to prescription use under the market rules postulated above. In addition to the implications for patient care, these restrictions would, for some companies, have severely eroded the capacity to finance research and development – for example, the manufacturer of the leading non-steroidal anti-rheumatic in 1984 was dependent on the product concerned for 84 per cent of its revenue from the UK market in that year. In addition to limiting therapeutic options and reducing the volume of funds that might be allocated to research and development programmes, action to



**Table 12** Leading medicine on the most valuable ten pharmaceutical sub-markets in 1984, analysed by timing of market entry and contribution to manufacturers' revenues

Therapeutic sub-market	Year of launch	Whether or not fourth or even later introduction in the relevant chemical class	Sales in 1984 as per cent of total sales of manufacturer
Antirheumatic non-steroids	1973	yes	84
Bronchodilators and other anti-asthmatics	1969	no	56
Beta blockers (plain)	1976	yes	65
Non-narcotic analgesics and anti-pyretics	1964	yes	56
Anti-peptic ulcerants	1976	no	76
Myocardial therapy	1977	no	73
Broad spectrum penicillins	1972	yes	76
Diuretics (other than thiazides)	1962	no	69
Beta blockers (combinations)	1979	yes	25
Thiazides	1970	no	36

Source: Based on IMS data

restrict market entry would entail a series of more generally negative consequences for pharmaceutical progress. Foremost, it would add to the risks of investing in innovation. The latter are already of considerable magnitude. It is estimated that between £50 million and £100 million is required to be spent over a period of 10 years or more in order to bring a new chemical entity from the laboratory to the market. Candidate medicines can of course fail at any point in the development phase and even after market launch success – that is, an appropriate return

on the sum spent on research and development – cannot be guaranteed because of such possibilities as the unforeseen emergence of unacceptable side effects, the arrival of powerful competitor products or unfavourable shifts in therapeutic fashion. To limit access to the market to the first few products in a chemical class would clearly add greatly to these existing risks. An individual manufacturer could not, for example, be certain that a product under development would reach the market in time – the evolutionary phase of a new medicine is subject to the possible occurrence of unpredictable setbacks. A delayed arrival might mean a failure to gain market entry and thereby entail a substantial loss on the resources that had been channelled into the preceding research and development programme. It may be speculated that under these circumstances some manufacturers might perceive the risks attached to pharmaceutical research to have reached unacceptable heights, resulting in decisions to relocate innovative investments in more secure areas of activity.

Developments along these lines would obviously diminish the overall resource input into pharmaceutical research and development and this in turn would be expected to cause a decline in new chemical entity productivity. At the same time, there exists a theoretical danger that artificial market constraints of the type described would have a negative impact on the 'quality' of new product developments. For example, in order to maximise the chances of reaching the market in time, manufacturers might effectively be denied the opportunity fully to develop the therapeutic potential or other advantages of their candidate medicine. And once a place on the market had been successfully realised there would presumably be little incentive to sustain the research effort in order to develop an improved extension of the original medicine. If all permitted market positions had been taken up there would axiomatically be no room for another product. In the example of the beta blocker market this

**Table 13** Examples of new uses for medicines discovered after marketing

<i>Extension of Therapeutic Use into New Areas by Application of Known Pharmacological Actions</i>	
Aspirin and NSAIDs as inhibitors of platelet clumping	– prevention of formation of arterial thrombi
Oestrogen and progesterone as inhibitors of ovulation	– oral contraceptives
Topical steroids as anti-inflammatory agents	– aerosols for asthma
<i>Unexpected New Therapeutic Uses Discovered by Chance (serendipity)</i>	
Iproniazid used in tuberculosis	– antidepressant effects, forming the first antidepressant
Chlodiazepam as a muscle relaxant	– anti-anxiety effects and the first benzodiazepine
Chlorpromazine as an antihistamine	– effective in schizophrenia giving the first antipsychotic drug
Minoxidil for hypertension	– increased hair growth forming a topical treatment for baldness in men
Sulphonamides for bacterial infections	– oral anti-diabetics and diuretics

Source: Snell, 1988

situation would clearly have had major implications for the later development of sustained-release formulations.

Patterns of pharmaceutical innovation observed to date suggest that market size limitation and thus the effective discouragement of post marketing research and development could be associated with therapeutic losses on an even broader scale. This possibility is implied by the contents of Table 13 which catalogues a number of important new pharmaceutical treatments that have emerged as a result of continuing research with selected medicines after they had entered use for their original indications. Returning to the specific example of the beta blocker market, it is also noteworthy that the valuable role these medicines now play in the treatment of glaucoma and as a means of promoting survival after myocardial infarction became apparent from research conducted on products that were not among the first three to enter clinical use.

A series of other costs may be linked to market modifying policies which as a by-product create disincentives to sustained post marketing research. It is arguably less likely, for example, that manufacturers will focus long-term attention on particular therapeutic areas with the consequent loss of specific centres of expertise in the industry. A further problem is raised by the possibility of products having unexpectedly to be withdrawn from use. In the example of the beta blocker market the third entrant suffered this fate and had a hypothesised three product limit been in operation there would have been major implications for prescribing options. Manufacturers would already have switched research resources away from this area of therapy, perceiving it to be a 'completed market', and a replacement product might not have been forthcoming for a potentially considerable period of time. Finally, multiple research efforts in particular therapeutic areas not only generate new medicines but play a part in promoting better understanding about the processes of disease. In addition to their therapeutic role, medicines function directly as research tools so that discouragement to the plurality of pharmaceutical research could slow down the progress of knowledge that eventually paves the way for the development of new and better medicines.



## Conclusion

This paper has attempted to demonstrate, via analyses of two annual cohorts of NCE introductions and a specific study of the beta blocker sub-market, that ICE medicines play a highly significant role in pharmaceutical innovation. One of the major points to emerge is that the long-term worth of a new medicine is extremely difficult to gauge at the time of market launch. There is a tendency to assume that late arrival in a particular therapeutic sub-market – that is, after perhaps three, four or more products have already become established in prescription use – is synonymous with unnecessary duplication. Yet evidence from the beta blocker market indicates that later introductions may, with the accumulation of clinical experience over time, emerge as more valuable therapeutic entities than those of longer standing availability. Barriers to market entry based crudely on some notion of appropriate market size therefore risk depriving patients of treatments that are potentially more effective than those to which they currently have access. More fundamentally, such restrictions would substantially undermine one of the essential foundations of innovative competition in pharmaceuticals – the development of new medicines from research based on existing products – and, as a result, the prospects for therapeutic progress in the future.

The economic significance of ICE medicines in pharmaceutical innovation has also been addressed in the paper. New chemical entities characterised in this way have been shown to contribute a substantial part of the current revenue pool from which manufacturers finance research and development activities. Without the resources derived in this way, many companies would not be in a position to sustain a viable level of investment in innovation.

The strengths of the conclusions drawn from the market data analyses are of course sensitive to the criteria that are applied in defining an ICE medicine. For example, relocating some of the new chemical entities included in the cohort study away from the ICE classification to the novel compound group would obviously diminish the significance of ICE medicines in providing funds for research and development. It is inevitable that disagreement will exist between different authorities with regard to the correct classification of some new chemical entities but this does not invalidate the fundamental point that ICEs are central to the economics of pharmaceutical innovation.

A further objective of this paper has been to expose a number of concerns about the relevance of the term 'me-too' in the context of pharmaceutical innovation. On one level, its use might be questioned because it is an umbrella expression which fails to differentiate between chemical entities that more refined analysis

would show to be located at various points along a hypothetical spectrum of innovativeness. It also obscures the fact that 'me-too' advances can pursue a number of different directions. Much incremental advance in the anti-infective field, for example, has been due to improved means of administration and efficacy whereas among the beta blockers it has manifested in the presence or otherwise of peripheral pharmacological actions. In the case of non-steroidal anti-inflammatories, the relatively small differences between many of the available products are countered by surprisingly large – and unexplained – variations in patient responses to this type of medication.

On a more fundamental level, it is clear that new chemical entities can by definition, be differentiated from one another on grounds of chemical composition. Once they have entered clinical practice their therapeutic advantages and drawbacks become apparent and this serves to widen yet further the interproduct differences noted from the original viewpoint of structure. Strictly speaking, therefore, the term 'me-too' appears quite simply to be inaccurate in the context of pharmaceutical innovation.

Observations such as these have stimulated attempts to find alternatives to the term 'me-too'. One example in this respect is 'me-better'. Whilst the latter succeeds in eliminating any suggestion of direct duplication, it remains misleading in so far as a new medicine need not necessarily constitute an improvement on existing products but may instead extend the range of therapeutic possibilities. It has therefore been proposed in the present paper that the term 'innovative chemical extension' (ICE) should be adopted for describing new medicines that cannot be categorised as novel or core innovations. The word 'innovative' conveys the idea of a new research based medicine and avoids any notion of duplication whilst 'chemical extension' suggests an addition to therapeutic options without implying any judgement about value (which, as this paper has shown, cannot be determined until a medicine has been 'evaluated' in clinical use).

Discussion about terminology would arguably be of little importance if it were merely a matter of semantic debate. It does, however, have a more serious bearing since use of the term 'me-too' implies a misunderstanding of the nature of pharmaceutical innovation and this in turn might conceivably encourage market interventions – such as placing limits on the allowable number of medicines belonging to a given chemical class – that ultimately could prove seriously damaging to therapeutic progress. With regard to this possible policy initiative, the present paper has shown that such intervention is quite simply unwarranted. Clinical experience over

the medium to long term effectively determines the relative value of different medicines without risking the potential therapeutic losses that might arise under a system of bureaucratic control. Such interference with the market would also damage the economic infrastructure sustaining pharmaceutical innovation. In this respect not only would the prospects for improved disease management be harmed but the future of one of the United Kingdom's most successful high technology industries – in 1988 pharmaceutical companies will achieve a positive balance of trade second only to that of the oil industry – could also be put in jeopardy.



# References

Association of the British Pharmaceutical Industry (1988). *The Pharmaceutical Industry and the Nation's Health*. London: ABPI.

Association of the British Pharmaceutical Industry (1988a). *British Medicines Research 1988*. London: ABPI.

Centre for Medicines Research (1987). *CMR Slides for the Pharmaceutical Industry*. Carshalton: Centre for Medicines Research.

Department of Health and Social Security (1983). *Report to the Secretary of State for Social Services of the informal group on effective prescribing (Greenfield Report)*. London: DHSS.

Drummond M F, Teeling Smith G and Wells N E J (1988). *Economic Evaluation in the Development of Medicines*. London: Office of Health Economics.

Lumley C E, Prentis R A and Walker S R (1987). *Pharmaceutical Medicine*, 2, 137–49.

Office of Health Economics (1975). *The Canberra Hypothesis, The economics of the prescription medicine market*. London: OHE.

Parrish J A, Lumley C E and Walker S R (1987). *Survey of Research and Development Expenditure by Pharmaceutical Companies in the UK between 1982 and 1986*. Carshalton: Centre for Medicines Research.

Reekie W D (1979). *Pricing New Pharmaceutical Products*. Beckenham: Croom Helm.

*Scrip* (1988). *New cardiovascular therapies discussed*. No 1320, June 24, p 28–29.

Snell E S (1988). *Pharmaceutical Medicine*. In press.

Wyke A (1987). *Molecules and Markets – A survey of pharmaceuticals*. *The Economist*, 7 February.

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