Pharmaceutical innovation by the seven UK-owned pharmaceutical companies (1964–1985)

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1 A total of three hundred and nineteen new chemical entities (NCEs) were investigated in man for the first time between 1964 and 1985 by seven UK-owned pharmaceutical companies. The majority (96.2%), were self-originated by the UK company or one of its overseas subsidiaries.

2 There was an increase in the number of NCEs investigated each year in man, doubling from an average of 12 per year up to 1980, to over 20 per year between 1981 and 1985. The majority of first drug evaluations in human volunteers were carried out in the UK (92.2%), in contrast to evaluation of new medicines in patients, where 42.9% were first tested outside the UK.

3 The majority of NCEs evaluated in man (78%), were in four therapeutic classes: anti-infectives (32%), anti-allergics (22%), drugs acting on the central nervous system (13%) and cardiovascular system agents (11%).

4 By the end of 1985, 49 (15.4%) of these NCEs had been marketed in the UK and 198 (62.0%) discontinued from further development. The main reasons for termination were inappropriate pharmacokinetics in man (39.4%), and lack of clinical efficacy (29.3%).

5 Average development times increased from less than 2 years between 1964 and 1965, to around 8 years in the 1980s with a consequent reduction in the effective patent life.

Keywords innovation new chemical entity pharmaceutical industry research and development success rate

Introduction

The United Kingdom is one of the major countries innovating pharmaceutical compounds, with an enviable record of new medicines in a number of therapeutic areas. It ranks amongst the top six countries involved in pharmaceutical research along with the USA, Japan, West Germany, France and Switzerland and was fourth in the international league with respect to research and development expenditure during 1982 (Chew *et al.*, 1985).

The process of pharmaceutical innovation is complex and measures of research and development output are important in understanding trends in drug development and the effects of changes in regulatory policies, such as the

impact of the Clinical Trials Exemption (CTX) scheme introduced in 1981 (Speirs & Griffin, 1983). Several indices for quantitative measurement of innovation have been proposed (Walker 1982; Wardell & DiRaddo, 1980), including the number of new chemical entities (NCEs) synthesised, and the number of patents issued. A more frequently employed assessment has been the number of NCEs reaching the market (Steward & Wibberley, 1980; Reis-Arndt, 1975, 1982). For a comprehensive evaluation, the quality of innovation or therapeutic value should also be ascertained, but in practice it is very difficult to quantify as existing measures are limited. Firstly because there are no common

scales of measurement and secondly, the full pharmacological and therapeutic potential of a new medicine may only become apparent several years after marketing. Additionally, some innovations are the result of cumulative improvement over several successive entries into a therapeutic area, with no one specifically identifiable pharmacological discovery.

The first step in pharmaceutical innovation involves discovery, design or synthesis of a new chemical entity but the earliest point at which it is possible to measure the output of the pharmaceutical industry relatively accurately is when the compound is first administered to man. The initiation of studies in human volunteers or patients represents the outcome of preclinical investigations and provides an important index of research activity related to the innovative process. It is also the first stage at which a compound can be considered a therapeutic candidate, and thus represents the most valuable, single measure of innovation.

A review of pharmaceutical innovation and trends in new drug development by seven UK-owned pharmaceutical companies over a 17 year period from 1964 to 1980 (Prentis & Walker, 1986) showed that a total of 197 NCEs were evaluated in man for the first time. The number remained fairly constant over this period, in contrast to the USA (Wardell *et al.*, 1978; Wardell & DiRaddo, 1980) and Switzerland (Mattison *et al.*, 1984), where there was a fall in the number of NCEs evaluated in man between 1961–1975 and 1960–1980 respectively. Of those innovated by the UK-owned companies, 137 were withdrawn and 35 (18%) marketed, the overall success rate of drugs innovated to those marketed was 5.6:1. Over 50% of the marketed medicines were concentrated in three therapeutic classes: the anti-infectives, drugs acting on the central nervous system and cardiovascular system agents, reflecting the pattern of innovation over the same period, measured as the number of NCEs first administered to man. With respect to introductions of new medicines into specific therapeutic areas, the new chemical entities marketed by the UK-owned pharmaceutical companies reflected trends in the UK industry as a whole (Griffin & Diggle, 1981), as well as that of the world market (Reis-Arndt, 1982). Griffin & Diggle (1981) suggest that there is a tendency to direct innovation for purely commercial returns rather than therapeutic need, resulting in the development of drugs in already crowded therapeutic areas. In contrast, Reis-Arndt (1982) states that if therapeutic categories are ordered according to 1980 market volume, most innovations are not necessarily in

the area with the highest subsequent sales.

Surveys of products marketed in the UK conducted by Steward & Wibberly (1980) and by Griffin & Diggle (1981), show increased drug development times for the UK industry as a whole. Prentis & Walker (1986) also demonstrated a doubling of development time between the 1960s and mid 1970s with a corresponding decrease in the effective patent life, from nearly 13 years to 6.5 years.

The present study reports on the process of innovation by seven major UK-owned companies, measured as the number of NCEs first administered to man and updates previous work in this area by 5 years, to include the period 1 January 1980 to 31 December 1985.

Methods

Confidential data on new chemical entities (NCEs) taken into man during the period 1 January 1964 to 31 December 1985 were collected from Beecham Pharmaceuticals; The Boots Company plc; Fisons plc; Glaxo Group Research Ltd; Imperial Chemical Industries plc; Reckitt & Colman plc and the Wellcome Foundation Ltd, using a specially designed questionnaire. The criteria for selection of NCEs were the same as previously described (Prentis & Walker, 1986) and differ from those of Reis-Arndt (1982) and Wardell *et al.* (1978) who both exclude biologicals. Reis-Arndt (1982) included esters which are excluded from this selection, unless development of the derivative conferred some major therapeutic benefit as assessed by the company producing the compound.

The type of information held on the computerised database is detailed in a previous publication (Walker *et al.*, 1986) and includes data on various aspects of innovation, from the date the NCE was first synthesized, through the various phases of development. Information was checked and validated where possible from alternative literature sources. An NCE with missing data relevant to a particular analysis was excluded from that analysis, but was included in other calculations for which the data were complete.

Results

During the 21 year period (1 January 1964 to 31 December 1985), a total of 319 NCEs were evaluated in man by the seven UK-owned research based companies and an additional

Figure 1 The number of NCEs innovated each year (number taken into man for the first time).

four compounds were taken on at the marketing stage for further development. The majority of the cohort studied (96.2%) were self-originated by the UK company (90.3%) or one of its overseas subsidiaries (5.9%), and only 3(1%) by a university or research body prior to development. The remaining 2.8% were either licensed from, or developed jointly with another company.

Between 1964 and 1980, the number of NCEs innovated per year fluctuated (Figure 1), averaging 12 per year, but since 1980 the numbers have doubled to over 20, with a record of 42 in 1983. This anomaly is due to the testing of 23 related compounds in one therapeutic class.

Most new drugs were first evaluated in healthy volunteers (93.4%), with an attrition ratio of 2.5:1 between testing in volunteers and patients. The majority of drug evaluations in human volunteers was carried out in the UK (92.2%), 5.6% in Europe and the remaining 2.2% in the United States and South Africa. In contrast, primary evaluation of new medicines in patients was carried out less frequently in the UK, only 57.1% of the total studied. The remainder were first investigated in Europe (35.3%), the USA and Canada (4.2%), or in India, Brazil and the Sudan (3.4%), with less than a third (27%) being

subsequently taken into UK patients. The sharpest decline in the number of NCEs evaluated per year in the UK, occurred after the mid 1970s (Figure 2), when the proportion first taken into patients abroad increased from an annual average of 18.4% of the total between 1964 and 1973, to 42% during the period 1974–1977, going up to 66% between 1978 and 1985. During 1984 and 1985 all initial drug evaluations in patients by the UK-owned companies were undertaken in Europe, except for one NCE which was tested simultaneously in the UK.

Figure 3 illustrates that of the total 319 NCEs taken into man, 49 (15.4%) had been marketed in the UK by the end of 1985, giving an overall success rate of those first taken into man to those marketed of 6.5:1, with 72 remaining in development. Of the 49 compounds marketed, 28.5% were anti-infectives, 20.4% drugs acting on the central nervous system and 12.2% cardiovascular system agents.

Examination of the success rate from clinical trial certificate (CTC) filing to product licence (PL) approval is shown in Figure 4. The NCEs are stratified into 5 year cohorts based on the year of CTC filing, 1965–1969, 1970–1974 and 1975–1979 where $n = 24$, 29, and 21 NCEs respectively. For each cohort, the success rate is expressed as the cumulative percentage of CTC

Figure 2 The number of NCEs taken into patients by year of innovation. ■, those first taken into patients in the UK, ▨, those first taken into patients overseas.

Figure 3 State of NCEs by year taken into man for the first time (innovated). ■, research terminated, ▨, in development □, marketed in the UK.

Figure 4 Success rate between filing of clinical trial certificate (CTC) and product licence (PL) approval. ○, 1965–1969 cohort, △, 1970–1974 cohort, □, 1975–1979 cohort.

filings that reach product licence approval at a given number of years after the date of the initial CTC filing. The last cohort studied ends in 1979 which allows 7 years for drugs to have reached approval. Success rates for cohorts after 1979 are not shown as too few years have passed since initial CTC or CTX filing.

Both the 1965–1969 and 1970–1974 cohorts show similar success rates in the first 2 years, reaching 50% and 45% respectively 7 years after initial CTC filing. For the 1975–1979 cohort, the initial success rate has dropped considerably to only 28.5% after 4 years, compared with 45.8% and 34.5% for the two previous cohorts, with no more product licence approvals after 7 years. During the period of study, CTC filings were fairly steady, averaging 4 per year with the time interval between filing and approval doubling from an average of 2.5 months between 1965 and 1969 to almost 5 months in the period 1970 to 1974, increasing further to 6.5 months between 1975–1979. After 1981, following the introduction of the CTX scheme, the number of CTX filings averaged 7 per year with a considerable shortening of the time interval between application and approval, to just over 1 month.

A total of 198 NCEs (62.0%) were withdrawn from development during the period under investigation, 72.2% during evaluation in volunteers and 27.8% after they had been taken into patients. Reasons for withdrawal are given in Table 1, the primary cause being inappropriate pharmacokinetics in volunteers (39.4%), followed by lack of clinical efficacy (29.3%). The large number failing because of pharmacokinetics is due to the therapeutic composition of the database, 30% of which comprises anti-infectives. These compounds pass quickly through the pre-clinical testing phases for two reasons: their relatively low toxicity and the possibility of accurately predicting their activity *in vitro*, but may subsequently fail due to lack of absorption when taken into man. All NCEs withdrawn because of animal toxicity (11%), had already been taken into volunteers and 10 had been granted a CTC or CTX for clinical evaluation in patients. Incidence of adverse reactions was the fourth most common reason for termination (10%), 33.3% of these being withdrawn during testing in volunteers, the rest during clinical trial studies. If the anti-infectives are removed from the cohort of those terminated

Table 1 Reasons for withdrawal of drugs from development.

Year taken into man	Number terminated	PK	EF	TO	AE	CI	IC	BE	CH	Reason not known
1964	3	2				1				
1965	8	6			1	1				
1966	6	3	2		1					
1967	5	3			1	1				
1968	6	3	1			2				
1969	9	6	2		1					
1970	13	10	3							
1971	12	7	2	1	1	1				
1972	12	6		2	3	1				
1973	8	1	4		3					
1974	13	8	2	1	1				1	
1975	7	3		1	2	1				
1976	6	1	3	1			1			
1977	6	2	4							
1978	5		2	1	1		1			
1979	11	3	5	2	1					
1980	10	3	2	3				1		1
1981	6	3	1		1					1
1982	10		6	2			1			1
1983	28	5	16	4		2	1			
1984	12	3	3	4	1			1		
1985	2				2					
Total:	198	78	58	22	20	10	4	2	1	3
Volunteers:	143	78	35	12	7	4	2	2	-	3
Patients:	55	-	23	10	13	6	2	-	1	-

PK Pharmacokinetic difficulties, EF Efficacy not proven,

TO Animal toxicity, AE Adverse reactions (humans),

CI Limited commercial interest, IC Improved candidate found

BE Budget exhausted, CH Chemistry.

and the reasons for termination re-examined, then lack of clinical efficacy accounts for over 50% of the remaining drugs.

The number of marketed NCEs discontinued in the 10 year period 1964–1973 was five out of a total of 29 marketed, a higher proportion than in the 12 year period 1974–1985, when only one of the 20 marketed compounds was withdrawn; all these drugs having an average life on the market of around 6 years. The main reason for withdrawal was due to reports of unacceptable adverse events and of the six products in question, two were cardiovascular drugs, two anti-inflammatories, one a central nervous system drug and the last an anti-infective.

The therapeutic distribution of NCEs first taken into man was examined using the classification of Drury *et al.* (1978) (Figure 5). The main therapeutic classes represented in the group were the anti-infectives (32%), anti-allergics (22%), drugs acting on the central nervous system (13%) and cardiovascular system agents (11%). Accompanying the increased numbers innovated per year during the

1980s, there have been changes in the rate of innovation in some of the therapeutic classes. Whilst this has been fairly constant within the anti-infective class during the 20 year period studied, there was some concentration around the early 1970s, and increased activity in this area during the 1980s. Increased innovation in the cardiovascular area first noted in the 1970s appears to be continuing, as does the patchy, but fairly even spread of NCEs evaluated in the central nervous system class.

There has also been increased innovation of anti-allergics since the early 1980s. Alternatively there has been very little activity in musculoskeletal, obstetrics and gynaecology or endocrinology areas, but increasing activity in the gastrointestinal class since the mid 1970s, and renewed interest in antineoplastics since the early 1980s.

Examination of estimated development times (date of patent filing to date of UK marketing) (Figure 6), which were available for 45 of the 49 marketed NCEs, indicates an upward trend for this small group. The time to develop a new

Figure 5 Trends in NCEs innovated by therapeutic class. Key to therapeutic classes: 01 gastrointestinal, 02 cardiovascular, 03 respiratory system, 04 nervous system, 05 anti-infectives, 06 vaccines, 07 endocrine system, 08 obstetrics and gynaecology, 09 anti-neoplastics and immunosuppressants, 10 anaemia and nutrition, 11 musculo-skeletal disorders 12 ear, nose and eye, 13 anti-allergics, 14 skin.

Figure 6 Estimated development time (EDT) of marketed NCEs by year of UK marketing. No NCEs were marketed in 1971, 1980 or 1984. □, 3 year moving average. n = no. of NCEs marketed each year.

medicine increased fourfold from less than 2 years in 1964-5, to around 8 years in the 1980s, reflecting increased time spent in preclinical, clinical and regulatory phases. If development times are calculated substituting the date of first marketing anywhere in the world for the date of marketing in the UK, similar times are obtained for this cohort.

Discussion

Innovation in the pharmaceutical industry has special significance because of its direct effects on human health, with the development of new drug therapies playing a key role in medical progress. The innovation of medicines is a multi-faceted procedure and the present study reinforces the necessity to study a number of indices when examining this process. In many investigations the number of NCEs marketed per year has been used as the sole basis for assessing innovation, whereas it is shown from these data that only 15.4% of those taken into man reach the UK market.

Between 1964 and 1985 the UK-owned companies continued to be involved almost exclusively with the development of compounds synthesised in their own laboratories. Very few NCEs originated from foreign-owned companies, or were obtained under licence to be subsequently developed by the UK-owned company. This is contrary to the finding in the United States by Mattison *et al.* (1987), where acquired NCEs account for an increasing proportion of those developed by US firms.

The number of clinical trial certificates (CTCs) issued in the United Kingdom had almost halved from 170 in 1972 to 87 in 1980 (Griffin & Diggle, 1981). In this study the number of CTCs filed was fairly constant through the period of study, and following the introduction of the Clinical Trials Exemption (CTX) scheme during 1981, there were 75% more CTX applications each year compared to CTC filings in previous years. This upward trend being in line with the UK industry as a whole (Speirs & Griffin, 1983; Speirs *et al.*, 1984). However the change in regulations did not result in early clinical work in patients being carried out in this country by the seven UK-owned companies. This finding is in contrast to the increased number of early clinical studies being conducted in the UK generally, by the whole of the UK industry (Griffin, 1982). At the present time, this new system does not appear to have speeded up overall development times, despite modified data requirements for submission

which allow a phased approach to clinical evaluation, so that patient studies can be extended as more laboratory safety data become available. However the impact of the CTX scheme may not become apparent until the late 1980s.

The UK-owned companies have been responsible for marketing 49 drugs during the period of study, and for evaluating over 300 NCEs in man, with the number of NCEs innovated per year during the early 1980s increasing, continuing a trend which had become evident by the late 1970s. This may result in more NCEs reaching the market in later years, but any effect will probably not be apparent until the 1990s.

The main reasons for NCEs innovated during the past 20 years being dropped from development were pharmacokinetic difficulties in man or lack of clinical efficacy. If the anti-infectives were excluded, then lack of clinical efficacy became the prime reason for termination. The proportion of NCEs taken into volunteers that were subsequently taken into patients was around 30%, this significant drop-out rate suggests that pharmacological animal models may require improvement alternatively it may reflect differences in physiology between man and animals, making accurate prediction of efficacy difficult.

Termination of drug development at various stages in the process resulted in an attrition ratio of those innovated to those marketed of 6.5:1. This is similar to the 5.6:1 reported for the period up to 1980 (Prentis & Walker, 1986), and is better than the 10:1 ratio reported for the United States (Wardell & Scheck, 1982), or 13.5:1 for the Swiss companies (Mattison *et al.*, 1984). Reduction in the number of marketed drugs being withdrawn after 1974 may signal improvement in certain aspects of toxicological and clinical screening or in regulatory procedures. This change is in line with the trend seen in the whole of the UK market (Hass *et al.*, 1985) and indicates that some aspects of pharmaceutical innovation and screening may be improving.

This study on pharmaceutical innovation by UK-owned companies shows that development times are continuing to increase, with a significant impact on the effective patent life of marketed products, which has been eroded from 11.5 years in the 1960s to approximately 8 years in the 1980s (excluding Licence of Right extension). The same trend has been observed for all NCEs marketed in the UK between 1960 and 1983 (Walker & Prentis, 1985; Walker *et al.*, 1986). Product licence approvals are also appearing later after CTC filing and the clinical

evaluation of new medicines has become more time consuming. Although the exact reasons are uncertain, there are probably a number of contributing factors, such as increased demands for pharmaceutical and toxicological data, higher scientific and technical standards, the tackling of inherently difficult disease conditions, increased complexity of clinical evaluation and administrative delays. However this lengthening of development times does not appear to be significantly affecting overall success rates in terms of the number of NCEs reaching the UK market.

The amount of research occurring in specific therapeutic categories has changed over the survey period. This shift in therapeutic focus may affect the NCEs which become available in the future, indicating that the industry is continually moving its research interests to meet requirements. In this study period, the most pronounced increases in activity were in the anti-allergic class since the 1980s and in the cardiovascular area since the mid 1970s. The number of medicines being studied in other categories has also changed, but the major contribution to the total research effort continues to be made by the anti-infectives, anti-allergics, drugs acting on

the central nervous system and cardiovascular system agents, as was noted previously (Prentis & Walker, 1986).

This update indicates continuing trends with respect to innovation and success rates. It has also demonstrated that the seven UK-owned research-based companies have continued to be a major source of NCEs, making a significant contribution to the total number of medicines marketed in the UK (Prentis *et al.*, 1987). It is encouraging that since the early 1980s, these companies have been evaluating an increasing number of NCEs in man. However with development times for marketed medicines increasing as demonstrated for this cohort and for all NCEs marketed in the UK (Walker *et al.*, 1986; Prentis *et al.*, in preparation), it will be the 1990s before the impact of this trend can be examined in terms of the number of medicines reaching the UK market.

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References

- Chew, R., Smith, G. T. & Wells, N. (eds) (1985). *Pharmaceuticals in seven nations*. London: Office of Health Economics.
- Drury, V. M. W., Wade, O. L., Beeley, L. & Alesbury, P. (eds) (1978). *Treatment—a handbook of drug therapy*. London: Kluwer Medical Press.
- Griffin, J. P., & Diggle, G. E. (1981). A survey of products licensed in the United Kingdom from 1971–1981. *Br. J. clin. Pharmac.*, **12**, 453–463.
- Griffin, J. P. (1982). Six months experience of the new procedure affecting the conduct of clinical trials in the UK. *Br. J. clin. Pharmac.* **13**, 253–255.
- Hass, Jr., A. E., Portale, D. B. & Grossman, R. E. (1985). New drugs: Their market life and safety. *Pharm. J.*, **234**, 235–238.
- Lumley, C. E., Prentis, R. A., Walker, S. R., (1987). Trends in research and development expenditure by the UK pharmaceutical industry (1982–84). *Pharm. Med.* (in press).
- Mattison, N., Thomas, E., Trimble, A. G. & Wardell, W. M. (1984). The development of self-originated new drugs by Swiss Pharmaceutical Firms, 1960–1980. *Reg. Tox. Pharmac.*, **4**, 157–173.
- Mattison, N., Trimble, A. G. & Lasagna, L. (1987). New drug development in the United States 1963–1984. *Clin. Pharmac. Ther.*
- Prentis, R. A. & Walker, S. R. (1986). Trends in the development of new medicines by UK-owned pharmaceutical companies (1964–1980). *Br. J. clin. Pharmac.*, **21**, 437–443.
- Reis-Arndt, E. (1975). New pharmaceutical agents 1961–1973. *Drugs made in Germany*, **18**, 123–130.
- Reis-Arndt, E. (1982). 20 Jahre Arzneimittelentwicklung – lung – Neue pharmazeutische Wirkstoffe 1961–1980. *Pharmac. Ind.*, **44**, 1115–1121.
- Speirs, C. J. & Griffin, J. P. (1983). A survey of the first year of operation of the new procedure affecting the conduct of clinical trials in the United Kingdom. *Br. J. clin. Pharmac.*, **15**, 649–655.
- Speirs, C. J., Saunders, R. M. & Griffin, J. P. (1984). The UK Clinical Trial Exemption scheme – its effects on investment in research. *Pharm. Int.*, *Oct.*, 254–256.
- Steward, F. & Wibberley, G. (1980). Drug innovation – what's slowing it down? *Nature*, **284**, 118–120.
- Walker, S. R. (1982). Innovation and drug development – Can the process be expedited? *BIRA Journal*, **1**, 34–42.
- Walker, S. R. & Prentis, R. A. (1985). Drug Research & Pharmaceutical Patents. *Pharm. J.*, **234**, 11–13.
- Walker, S. R., Prentis, R. A. & Ravenscroft, M. K. (1986). Innovation as assessed by new pharmaceutical compounds marketed in the United Kingdom between 1960–1983. *Pharm. Int.*, *June*, 135–7.
- Wardell, W. M., Hassar, M., Anavekar, S. N. & Lasagna, L. (1978). The rate of development of new drugs in the United States, 1963 through 1975. *Clin. Pharmac. Ther.*, **24**, 133–145.
- Wardell, W. M. & DiRaddo, J. (1980). The measure-

- ment of pharmaceutical innovation. *J. clin. Pharmac.*, **20**, 1–9.
- Wardell, W. M. & Sheck, L. E. (1982). Is pharmaceutical innovation declining?: interpreting measures of pharmaceutical innovation and regulatory impact in the USA, 1950–1980. *Presen-*

tation at the Arne Ryde Symposium on Pharmaceutical Economics. Helsingborg, Sweden.

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