Trends in the development of new medicines by UK-owned pharmaceutical companies (1964-1980)

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- 1 One hundred and ninety-seven new chemical entities (NCEs) were investigated in man for the first time between 1964 and 1980 by the seven UK-owned pharmaceutical companies.
- 2 Thirty-five of these NCEs have been marketed and 137 withdrawn from further research and development.
- 3 There was an increase in the number of NCEs investigated each year, but this was counter-balanced by an increase in the number rejected.
- 4 Development times increased from about 4.5 years in the 1960s to 9 years in the 1970s with an accompanying reduction in the effective patent life.

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

Introduction

The measurement of pharmaceutical innovation is of importance in understanding the process of drug development and determining the performance of the Pharmaceutical Industry. The identification of any trends in innovation is of interest both in the formulation of regulatory policies and the elucidation of problems so that, if necessary, remedial action may be taken.

When assessing innovation it is vital to define accurately the terms employed and determine both its quantity and quality. Pharmaceutical innovation has been defined as any development which is intended to produce a therapeutic advance (Wardell & DiRaddo, 1980) and that relating to medicines is considered in this study. Measures both of the number of therapeutic advances and the relative value of innovations have been proposed and any one, or a combination of them, can be used in this assessment. Research input may be measured by a number of objective determinants, including analysis of the number of new chemical entities (NCEs) synthesised and the number of patents filed or issued. The number of NCEs undergoing pharmacological screening or evaluation in man represents a means of measuring the next stage

in the process, whereas the number of product licence applications submitted or products marketed, measures research output. Evaluation of the quality of an innovation, i.e. whether a compound is fully-, semi- or non-innovative, is subjective and has limited value as the full pharmacological and therapeutic potential of an innovation can never be predicted at the time of its discovery.

On a worldwide basis the number of new chemically defined substances marketed for the first time as human or veterinary medicines has been examined by Reis-Arndt (1975, 1982). The number of new medicines entering the world market was shown to have steadily decreased from 93 in 1961 to 48 in 1980. The therapeutic areas with most introductions during the same period were anti-infectives, non-steroidal anti-inflammatories, anti-neoplastics, cardiovascular and central nervous system drugs. Trends in the marketing of NCEs in the United States have also been studied and the yearly rate was seen to have dropped from over 70 in 1960 to less than 20 in the 1970s (Wardell *et al.*, 1978, 1980). Surveys of products marketed in the United Kingdom have been conducted by Steward & Wibberly

(1980) and Griffin & Diggle (1981). The former demonstrated a substantial decline in the annual rate of introduction of brand-name pharmaceutical products during the period from 1960 to the mid-1970s. In the early 1960s approximately 300 different products were introduced per year, of which 30–40 were NCEs, and in the late 1970s this figure had declined to about 100 per year (15–20 NCEs). Development times were also shown to have increased, but interestingly the number of withdrawals from the market significantly decreased after 1964 and the authors related this to the establishment of the Committee on Safety of Drugs.

An NCE is considered a potential therapeutic candidate when it is tested in man for the first time. The most valuable single measure of innovation is, therefore, to study the number of NCEs first administered to man. This has been examined in the United States by Wardell *et al.* (1978, 1980). The resulting data indicated a fall in the number of NCEs taken into man over the period 1961–75 and the distribution within therapeutic areas was similar to that demonstrated by Reis-Arndt (1975, 1982) for the world market. Similar results have also been reported for the Swiss Pharmaceutical Industry, showing a decline from over 80 NCEs innovated in 1960 to just over 20 in 1980 (Mattison *et al.*, 1984). These studies in the USA and Switzerland have also demonstrated increasing times for the different phases of NCE development which have been equated with changes in national regulations.

A similar survey of NCEs innovated by the research-based pharmaceutical companies in the UK was undertaken to cover the past two decades, a period of regulatory change (Prentis & Walker, 1984). The aim of these surveys is to study any changes in the rate and subject of innovation and to identify possible causal factors.

Methods

In the study the number of NCEs tested in man during the period 1 January 1964 to 31 December 1980 was examined and their progress was followed through the various developmental stages, either until research terminated, or the NCE was marketed in the UK. A new chemical entity was defined as 'a new chemical or biological compound tested in man for therapeutic purposes for the first time' and excluded new salts or esters unless they conferred some additional therapeutic advantage. This definition differed from that used by Reis-Arndt and Wardell who both excluded biologicals, but excluded esters included by Reis-Arndt. The administration of an NCE to

man for the first time for therapeutic purposes was taken as the determinant of innovation (Ravenscroft & Walker, 1983).

A comprehensive questionnaire was used to collect data on various aspects of the innovatory process from the date the NCE was first synthesised (including details of the company/research body and country of origin), through the various stages of animal and clinical testing to the regulatory and marketing phases. Details were also requested of the UK patent application and term for marketed NCEs, the date of Product Licence applications and the date and reason for withdrawal of the products from further research or from the market. The seven UK-owned research-based pharmaceutical companies (Beecham Pharmaceuticals; The Boots Company plc; Fisons plc; Glaxo Group Research Ltd; Imperial Chemical Industries plc; Reckitt & Colman plc and The Wellcome Foundation Ltd) completed a questionnaire for every NCE which they had either tested in man, first taken to clinical trial in the UK or first marketed in the UK during the period under investigation.

The data were collated and managed using the Delta software package (from Compssoft plc) on ACT Sirius microcomputers. After checking and validating (where information was available from alternative sources) the data were returned to the source company for final verification and for any additional information before analyses were carried out. An NCE with data missing relevant to a particular calculation was excluded from that analysis, but was included in other calculations for which the data were complete.

Results

During the 17 year period from 1 January 1964 to 31 December 1980 a total of 197 NCEs were tested in man for the first time by the seven UK-owned research-based companies. At the time of analysis a total of 35 of the 197 NCEs was marketed in the UK giving an attrition ratio of those innovated to those marketed of 5.6:1. One hundred and thirty-seven NCEs had been withdrawn from further R&D and the remaining 25 were still in development although some of them may subsequently reach the market or be aborted which will alter the attrition ratio. However, if the same ratio was applied to this 25 then a further five might be expected to reach the market and this would alter the overall ratio to 5:1. One hundred and four of the 197 NCEs had been evaluated clinically, some of which were subsequently terminated, while others remained in development or were marketed. Over 94% of

the NCEs were originated by the UK company itself, 3% came from an overseas subsidiary of the UK parent and 3% were licensed from an overseas company or came from a university or research body.

The NCEs were grouped by therapeutic class according to the classification used by Drury *et al.* (1978) (Table 1). The main groups were anti-infectives (42%), drugs acting on the central nervous system (16%) and the cardiovascular system (10%), and those for allergic conditions (11%) (Figure 1). On average 11 NCEs were innovated per year by the seven companies and despite the variation between years there appeared to be an upward trend (Figure 2). Examination of the numbers for which active research and development had been aborted showed an average value of just over seven NCEs per year and a slightly steeper upward trend than for the numbers innovated (Figure 2). The graph of the cumulative number remaining in development (including those marketed), expressed as a percentage of the cumulative number tested in man, indicates a steady decline (Figure 3). Due to the 'start-up' effect the value for 1964 was excluded from the plot which demonstrates that although the number innovated is increasing yearly, the number aborted is increasing at a greater rate. This trend, if not halted or reversed, will clearly have a dramatic effect on the number of NCEs reaching the market in later years.

There was a change in the emphasis of innovation by UK companies with time (Figure 4) and although the total sample is small some trends are apparent. Within the anti-infective area there has been considerable activity throughout the period, mostly around 1970 with a tailing in the

later years. Innovation of cardiovascular drugs was also spread over the period studied, but there was increased activity in the late 1970s, unlike the CNS drugs which showed a patchy but general spread. The anti-allergic NCEs first appeared in this cohort in 1971 and although this class has since been the subject of a steady flow of innovation this is not reflected by the numbers marketed.

A major subset of the group consisted of the 137 NCEs for which research had been aborted (Figure 5). The main reasons for termination were problems with human pharmacokinetics (34%), lack of proven efficacy (15.7%) and adverse effects observed in human or animal tests (13.7%). The fact that inappropriate pharmacokinetics in man is the major cause for the termination of research in this group reflects the

Figure 1 Innovation by therapeutic class (for abbreviations see Table 1).

Table 1 Therapeutic classification after Drury *et al.* (1978)

Class	Abbreviation	Description
01	GI	Gastrointestinal
02	CVS	Cardiovascular system and diuretics
03	Resp	Respiratory system
04	CNS	Central nervous system
05	A-inf	Anti-infectives
06	Vac	Vaccines
07	End	Endocrine system
08	GU	Obstetrics and gynaecology
09	A-neo	Anti-neoplastics and immunosuppressants
10	Nut	Anaemia and nutrition
11	M-sk	Musculo-skeletal disorders
12	EN&E	Ear, nose and eye
13	A-al	Anti-allergics
14	Skin	Skin preparations
15	Misc	Miscellaneous drugs
16	Diag	Diagnostics

Figure 2 NCEs innovated and terminated by year (□, to man; ■, terminated).

Figure 3 The cumulative number of NCEs remaining in development as a percentage of the cumulative number innovated (□—□, raw data; —, line of best fit).

therapeutic composition of the overall database. Anti-infectives (which account for 42% of the database) usually pass quickly through the stages of animal testing due to their relatively low toxicity and the ability accurately to assess their microbiological activity *in vitro*. When an antibiotic designed for oral use is first tested in man its absorption may be unsatisfactory and the compound is then superseded by another drug candidate. If the reasons for termination of re-

search are examined with the anti-infectives excluded, the picture is very different from that of the group as a whole. Inappropriate pharmacokinetics was the reason for termination for only 5% of the remaining NCEs and lack of clinical efficacy was the most frequent reason (25.4%) with adverse reactions in man (11.4%) next. This was emphasised by an examination of the 'development life' of those NCEs for which research had been terminated. Development life was defined as the time between innovation and the termination of research and was plotted

Figure 4 Trends in NCEs innovated by therapeutic class (for abbreviations see Table 1).

Figure 5 Fate of NCEs. □, Marketed; ■, in development; terminated due to: ▨, adverse effects; ▩, toxicity; ▧, lack of efficacy; ▦, pharmacokinetic reasons; ▥, miscellaneous reasons.

for all the NCEs terminated, for anti-infectives and for the remainder (Figure 6). The curve for the anti-infectives can be seen to fall sharply, with an estimated half life of 0.5 years whereas for those not in this group the curve is considerably shallower and the half life was just under 3 years. Only three of the 65 anti-infectives for which research had terminated were ever given to patients.

A total of 35 of the 197 NCEs had been marketed in the UK by the beginning of 1984, three of which were subsequently withdrawn (two due to adverse clinical effects and one for commercial reasons). Examination of the therapeutic classes to which those 35 belong indicated,

Figure 6 Development life of NCEs terminated. Development life is defined as the time taken between the date of innovation and research being terminated. □, All NCEs terminated; ○, non-anti-infectives; ●, anti-infectives.

as expected, that there was a direct reflection of the pattern seen in innovation over the period (compare Figures 4 and 7). Although the sample size is small a definite upward trend can be demonstrated in the development times (from first synthesis to UK marketing) for those NCEs marketed. In the 1960s development time was 4.5 years and this had doubled for those marketed in the 1970s (Figure 8).

Discussion

There are several individual measures of innovation, the number of new chemical entities reaching the market being the most frequently employed (Steward & Wibberley 1980; Reis-Arndt, 1975, 1982). The present study, however, demonstrates the importance of examining more than one

Figure 7 Trends in NCEs marketed by therapeutic class (for abbreviations see Table 1).

Figure 8 Estimated development time (EDT) is defined as the time between filing of U.K. patent and U.K. marketing. No NCEs were marketed in 1971 and 1980. □—□, EDT; ---, line of best fit.

factor, when studying innovation, including the number of NCEs tested in man. Although the UK-owned companies have been responsible for marketing only 35 NCEs during the period of study, almost 200 NCEs were evaluated in man. Most of these were rejected because they did not satisfy the criteria of safety and/or efficacy. Between 1964 and 1980 the UK-owned research-based companies were 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 by Wardell *et al.* (1980) that cross-licensing by US-owned companies increased during the late 1970s.

The number of NCEs innovated during the 1970s increased with respect to the 1960s, but when coupled with a corresponding increase in the number of NCEs aborted, this resulted in a decline in the total number of NCEs remaining in development as a percentage of the number innovated (Figure 3). A continuation of this trend may result in fewer NCEs reaching the market in the late 1980s, although this has remained constant for the past two decades (Walker *et al.*, 1986). The study confirms that, whilst

scientific research in Universities and other establishments outside the pharmaceutical industry is important in the acquisition of basic scientific knowledge which ultimately contributes to drug discovery, only a very small percentage of NCEs originate from such sources. The majority (over 97%) of NCEs originated within the Industry itself.

The success rate for the UK-owned companies of 5.6:1 appears to compare favourably with that reported for the United States (10:1, Wardell & Scheck, 1982) and the Swiss companies (13.5:1 Mattison *et al.*, 1984). This means that for every five NCEs tested in man by the UK-owned companies one new medicine reached the market. The reasons for this favourable comparison are unknown, but may be related to the small number of compounds in the study, the therapeutic classes under investigation and the differing internal policies of the companies involved.

The decision to terminate research after several years of developmental work and considerable expenditure on R&D is usually taken if the potential safety or efficacy of the new medicine is found to be unsatisfactory. Research was terminated for approximately 70% of all the NCEs studied and, excluding the anti-infectives, most failed due to a lack of clinical efficacy (25.4%). This suggests that there is a need to improve pharmacological models in some therapeutic areas.

The doubling of development times during the period 1964–80 had a significant impact on the effective patent life of marketed products. This was eroded during the same period, having declined from 11.5 years in 1964 to 5 years in 1980 (excluding Licence of Right extension—Walker *et al.*, 1986), reducing the time during which the medicine was on the market with monopoly rights allowing for the recovery of R&D costs. Unless the trends of increasing development times, decreasing effective patent life and falling numbers of NCEs in development can be reduced, the prospects for new drug development in the future are a cause for concern.

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