THE COSTS AND BENEFITS OF REGULATING NEW PRODUCT DEVELOPMENT IN THE UK PHARMACEUTICAL INDUSTRY

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Foreword

This is the second in an occasional series of Pharmaceutical Industry Papers to be published by OHE. The first concerned prices;* this second paper is concerned, by contrast, with the costs of pharmaceutical innovation.

This study by Keith Hartley and Alan Maynard is based on a survey which they conducted amongst major pharmaceutical companies in Britain during 1980. It clearly identifies costs arising from the 1968 Medicines Act, in terms of money, manpower and delays.

Significantly, since the survey was carried out in 1980 there has been some relaxation of the regulations controlling the testing and marketing of new medicines. In particular, the delays to clinical trials which Hartley and Maynard reported have been substantially reduced by a scheme of exemptions from Clinical Trial Certificates in suitable cases.

The conclusions of the two authors suggest that there may, however, be further scope for relaxation of regulations under the 1968 Act in order to strike an optimum balance between costs and benefits in relation to the safety of new medicines. Indeed Hartley and Maynard go so far as to discuss the possibility of a return to a voluntary scheme for the approval of new medicines, such as operated effectively under the Committee chaired by the late Sir Derrick Dunlop.

Whether or not such an option is a practical political possibility, the present survey is important in quantifying some of the costs associated with the operation of the 1968 Medicines Act in 1980. It is published by OHE as a contribution to the continuing discussion on the proper balance to be struck in relation to the safety of medicines. This debate is particularly relevant in Britain, which along with Germany, Switzerland and the United States is one of the four countries in the world whose pharmaceutical innovation contributes not only to the well-being of mankind but also the national economy. In 1980, the positive balance of trade in pharmaceuticals in Britain exeeded £500 million. Any measures which might help to maintain or expand this contribution to national wealth need to be carefully considered.

George Teeling-Smith
Director OHE
January 1982

* Price Comparisons of Identical Products in Japan, the United States and Europe; W. Duncan Reekie

Preface

The UK Pharmaceutical Industry has become increasingly concerned about the effects of government regulation on its competitive position and economic performance. It has been asserted that regulation in the form of the Medicines Act 1968 is costly and is having an adverse effect on the Industry's research and development (R & D) performance. For example, it is claimed that the Act requires the employment of additional staff, results in adverse effects on innovation, longer development time scales for new drugs and firms undertaking R & D abroad rather than in the UK. The objective of this study was to examine the existence and magnitude of these effects and to develop a broad cost-benefit framework for evaluating the 1968 Medicines Act. The results presented in this study are the outcome of one of the few empirical economic investigations of the costs and benefits of UK regulatory arrangements.

The study was restricted to the regulatory system for *human* medicines—i.e. those parts of the 1968 Medicines Act and associated regulations which relate to humans. Part I of the study describes the 1968 Act and summarises some of the major policy issues. Part II presents the detailed Questionnaire evidence and supporting empirical work. Much of the material is original and forms the basis for our estimates of the costs of the 1968 Medicines Act.[1]

Part I: The Policy Issues

A INTRODUCTION

1 The extent of regulation in the UK

Since 1945, successive British Governments have intervened increasingly in the economy. The regulation of the behaviour of firms is one aspect of this trend towards state intervention in the private sector. Examples of such regulation include employment legislation, embracing contracts, employment protection, equal opportunities, health and safety at work, training and redundancy payments. There have been controls on prices, wages and profits involving minimum wages, equal pay, rent control, price regulation schemes (e.g. NHS drugs), profit rules on Government contracts and a Review Board for Government Contracts.[2] Policies have also developed towards monopolies, mergers, restrictive practices and consumer protection (e.g. the Fair Trading Act, 1973). Elsewhere, regulation has taken the form of Government licensing of entry, as with doctors, teachers, patents, public houses, taxis, road and air transport and the subject of this study, namely the Medicines Act, 1968.

2 The contribution of this study: a cost-benefit framework

Governments, politicians, civil servants and economists are fond of proposing regulation. But there are few empirical studies of the costs and benefits of regulation. *How costly is regulation? What are the costs of alternative regulatory systems including de-regulation? What are the likely benefits of regulation and do they exceed its costs?* This study estimates the costs and outlines the benefits of regulation in the form of the 1968 Medicines Act. On the cost side, evidence is presented on the effects of the legislation on testing requirements, development periods for new products and whether UK firms are increasingly undertaking R & D abroad. In particular, the Industry has criticised the Act for its 'excessive bureaucracy', reflected in 'too many and inefficient' testing requirements imposed on firms, and longer periods to obtain regulatory approval. The result is believed to be greater delays in the introduction of new drugs and hence a continuous decrease in the effective patent life of a new medicine. Evidence is presented on effects and their costs. The benefits side of the equation is more complex and controversial, since it requires a valuation of human lives.[3] We adopted a more modest and limited approach to this subject. Some of the possible benefits of the Act are considered, especially the implications for patient safety and the relevance of risk-benefit ratios. We then use our cost estimates to contribute to the public debate about the social desirability of the 1968 Medicines Act: *if it costs £X million per annum, does society believe that such expenditures are worthwhile* (i.e. would they be better spent on other things). Such a policy debate could lead to an identification of the cost-effective method of achieving social goals. Risks cannot be removed: how much are we prepared to pay to reduce risks and which policy alternative is cheapest?[4]

The study also has wider policy implications. Successive Governments have aimed to improve the international competitiveness of the UK economy, particularly in technically progressive industries. The 1968 Medicines Act is a classic example of Government efforts to regulate an R & D intensive and technically progressive Industry. The result is believed to have affected the magnitude and location of the UK Industry's R & D effort and the rate at which new products are developed and marketed. In other words, there are potential conflicts between industrial and regulatory policy. Thus, the study raises the general issue of whether the UK believes that it is worthwhile retaining a Pharmaceutical Industry of the existing size. An obvious starting point is a description of the Industry and the 1968 Act.

3 The UK Pharmaceutical Industry

The Pharmaceutical Industry has annual sales in excess of two billion pounds, is a major exporter and creator of a favourable balance of trade in drugs, spends a large amount of money on research and development, and provides a supply of new chemicals with novel therapeutic properties. Table 1 summarises some of the main statistics for the Industry. Further key features are:[5]

(a) Of the 83 major manufacturers in the UK Industry, 37 were US-owned, 31 were European-owned and 15 were British.

(b) The UK's major competitors in world markets are West Germany, Switzerland and the USA.

(c) It requires more than 10 years at an estimated cost of £20-30m to develop a new medicine prior to marketing. Typically, some 50% of the Industry's R & D is spent on basic and applied research. Such expenditures are risky and uncertain: usually out of

TABLE 1
The UK Pharmaceutical Industry £m, current prices

	1968	*1979*
Total output	292	2,060
Employment (numbers)	80,000	75,000
Exports	97	651
UK imports of pharmaceutical preparations and chemicals	20	257
Research and development	17	224
Profitability: return on capital for NHS sales (%)	23.0	19.5 (1977)

Source: ABPI, *The pharmaceutical industry and the nation's health*, London, 1980.

every 10,000-12,000 compounds studied, only *one* reaches the market! In such circumstances, firm behaviour will be affected by the patent life for a new product. Clearly, longer development time-scales and a fixed patent life reduces the period available for an innovator to obtain a return on its costly R & D. The 1977 Patents Act extended patent life from 16 to 20 years.

B THE MEDICINES ACT, 1968

The 1968 Medicines Act aims to protect consumers by improving the safety, quality and efficacy of drugs. These objectives are to be achieved through a licensing system, administered by the Department of Health and Social Security (DHSS) with advice from the Medicines Commission and its specialist Committees. The Act was a major departure from the UK's previous policy.

1 The history of Control: Thalidomide and Dunlop[6]

Before 1968, there were few statutory limitations on the freedom of firms to market new medicinal products in the UK. In fact, the need for legislation was being considered when, in November 1961, the effects of thalidomide were revealed. The resulting public concern and subsequent enquiry by a specialist medical advisory group led to the recommendation that an expert committee be established to review the evidence on new drugs and to offer advice on their toxicity. The result was a Committee on Safety of Drugs, established by the Health Ministers in 1963 with Sir Derrick Dunlop as chairman. The Committee started work on 1st January, 1964 and operated until September 1971.

The Committee on Safety of Drugs (CSD) had no legal powers. It operated with the *voluntary* agreement of the Association of the British Pharmaceutical Industry (ABPI) and Proprietary Association of Great Britain. Both organisations promised that their members would seek, and abide by, the advice of the CSD before undertaking clinical trials or marketing any new drugs. In this way, the CSD provided a *voluntary registration system* embracing scrutiny before clinical trial and marketing, as well as post-marketing surveillance for adverse reactions. This voluntary system was distinguished by a simple machinery and a lack of formal documentation, so that it '... was able to deal rapidly with submissions made to it'.[7] Critics of the voluntary arrangements claimed that firms were not legally obliged to submit their products for scrutiny; nor was there any machinery for the licensing and regular inspection of premises manufacturing medicinal products.

The specialist medical advisory group which recommended the establishment of the CSD, also made proposals for new legislation on drug safety. The eventual outcome was a White Paper *Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines,* published in September 1967. These proposals formed the Medicines Act, which became law in October 1968.

2 The Medicines Act, 1968

With its emphasis on safety, the 1968 Medicines Act appears to be a classic example of consumer protection legislation. It replaced most of the previous legislation on the control of medicines for human and for veterinary use. This study concentrates on humans. The Act covers most aspects of the control of medicines, the exceptions being price controls and special controls on narcotics and other drugs which may be misused.

The major features of the Act were:

(a) The creation of a Medicines Commission to advise Ministers on the execution of the Act and on medicinal products generally (e.g. child safety; information to patients). Typically, the Commission consists of about twenty members, some of whom must be doctors, veterinary surgeons, pharmacists, chemists and people with experience in the Pharmaceutical Industry.

(b) The establishment of *expert committees.* These are created by Ministers on the advice of the Medicines Commission and they consist of:

(i) The Committee on Safety of Medicines (CSM) which advises the licensing authority on questions of the safety, quality and efficacy of medicines for human use. It also collects, evaluates, and advises on any reports of adverse reactions to drugs. Like its predecessor (the CSD), the CSM scrutinises *before* clinical trial and marketing, as well as *after* marketing. In 1980, the CSM had 22 members.

(ii) The Committee on the Review of Medicines (CRM) was established in 1975, to review the safety, quality and efficacy of *existing* products on the British market. In 1980, the CRM had 23 members.

(iii) The British Pharmacopoeia Commission which prepares future editions of the British Pharmacopoeia containing all the published standards for human and veterinary medicines.

(iv) Further Committees specialise in Veterinary Products, and Dental and Surgical Materials.

(c) The introduction of a *licensing* system which regulates clinical trials, marketing, importation, manufacture and distribution of medicinal products. The Medicines Division of the DHSS acts as the licensing authority, with the CSM advising it on *new* drugs and the CRM on *existing* products. The current licensing procedure commenced in September 1971. Transitional arrangements operated until September 1972, whereby *existing* products on the market were automatically awarded *licences of right:* the aim, which is being achieved over time, is that such products will be eventually assessed by the CRM. About 36,000 products were given licences of right.

(d) The introduction of *restrictions on the advertising and promotion* of medicinal products, including labelling and containers.

3 The operation of the Act

The detailed operation of the Act is the responsibility of the Medicines Division of the DHSS. This Division:

(a) Acts as the licensing authority. There is an appeals procedure, including the possibility of appealing to the Medicines Commission.

(b) Acts as the enforcement authority. In particular, the Medicines Inspectorate of the Division inspects UK and foreign pharmaceutical manufacturers.

(c) Monitors adverse reactions. In this task it is assisted by a number of part-time doctors distributed throughout the country.

The public sector regulatory costs are partly financed by income from fees. The holders of certificates and licences issued under the 1968 Act are required to pay fees to meet part of the operating costs of the licensing system. Fee income is fixed at about 65 per cent of the civil service costs, together with a proportion of the costs of the various Committees, inspectorate and data processing. For 1980-81, income from licences was estimated to be £3.54 million.

4 The development of the Act

The legal framework of the 1968 Act has been supplemented and expanded by the power to make secondary legislation in the form of Regulations or Orders and to include appropriate conditions in licences. It is claimed that such arrangements allow the regulatory authority '... to develop a flexible and sensitive approach, in a spirit of partnership with all the other parties concerned, and not to allow the ossification and over-formalisation of regulation in a changing environment'.[8] The actual performance of the regulatory authority is assessed at various points in this study. However, the existence of secondary legislation means that our study has to embrace the operation of the 1968 Act and its associated regulations.

5 Summary

The UK approach to drug regulation has developed from a voluntary to a legal system with licensing arrangements. The approach involves both pre- and post-marketing controls, as well as restrictions on actual marketing behaviour (e.g. advertising). In other words, the 1968 Act aims to provide the basis of a totally comprehensive drug regulatory system. It monitors marketed drugs from the very earliest stages when the general public becomes involved in clinical trials, right through to when a product has been on the market and adverse reactions start to appear.[9] In this way, it aims to protect consumers by improving the safety, quality and efficacy of drugs.

C WHY REGULATE? THE ECONOMIC ARGUMENTS FOR THE 1968 MEDICINES ACT

The underlying policy model for the 1968 Medicines Act can be deduced from the objectives of the legislation and the operation of the associated licensing system. This suggests a case for state intervention based on propositions about 'market failure'. A second set of propositions can be constructed to explain the choice of a licensing system as the most appropriate form of regulation.

The case for state regulation is usually based on the following arguments:[10]

(a) Drugs are 'different' and consumers need protection.

(b) Private markets have failed to protect consumers (e.g. thalidomide).

(c) This market failure was reflected in:

(i) Inadequate testing.
(ii) Inadequate quality control.
(iii) Deficiencies in information (e.g. misleading claims).

Thus, the policy view was that before 1968, 'free' markets were providing drugs which were unsafe, of poor quality and of inadequate efficacy. Such alleged inadequacies were generating costs in terms of morbidity and mortality which could be avoided (at some, usually unspecified, cost). Consequently, it was believed that state intervention was required to 'correct' for these apparent market failures and 'improve' the situation. Having decided on legislative intervention, the Government had to choose its desirable form and quantity. Choices were needed as to which aspects of firm and market behaviour require intervention (e.g. regulation of prices, profits, non-price behaviour such as advertising, or of entry). The case of a licensing system as the preferred form of intervention followed from the beliefs about the causes of market failure. The advocates of the licensing system argued that:

(a) A voluntary system of regulation (e.g. Committee on Safety of Drugs) was unsatisfactory, and that legislation was needed to protect consumers and reassure the public. There were also international demonstration effects as comparisons were made with foreign regulatory systems such as those in the USA which had (fortuitously?) prevented damage from thalidomide, and had been established to remedy earlier 'market failures'.[11]

(b) Free entry into the drug market was a problem. Thus, the attractiveness of a centralised licensing system which would control entry and standardise safety conditions throughout the UK.

(c) Consumers (patients) need safeguarding since they are not experts and they are unable to assess the risks and benefits of drugs. The legislation claims to operate to the benefit of the *consumer*. It implies that the best way to protect the consumer is

to require firms to satisfy an independent body of experts as to the safety of a drug: hence the creation of the Medicines Commission and the expert committees to advise Ministers on licensing.

(d) Testing, manufacturing quality and information were at fault. If independent experts maintain that risks are likely to arise at all stages in the life-cycle of a drug, then statutory safeguards (i.e. legislative protection of consumers) must be comprehensive and wide-reaching. Thus, licences are required for clinical trials, marketing, manufacturing, importation and wholesaling of drugs. Also, the 1968 Medicines Act allows the Government to regulate labelling, descriptions, packaging and the advertising of drugs. Such a comprehensive drug regulatory system has not been without its critics.

D A CRITIQUE: WHAT IS WRONG WITH THE 1968 ACT?

Critics of the 1968 Act point to its excessive bureaucracy, its protection of the Industry, the confusion between intermediate and final outputs and the costs of the legislation. More fundamental problems arise because of the general lack of scientific evidence on the determinants of our health status.[12] We are relatively ignorant about the relative effectiveness of health care, drugs, education, income redistribution, housing, family care and other factors in producing a 'healthy life'. Similar problems arise in determining the effects of alternative regulatory arrangements for the Pharmaceutical Industry (cf USA and UK) on the output of 'healthy days'. Some of these criticisms are worthy of elaboration.

1 Excessive bureaucracy

Economic models of bureaucracy suggest that regulatory agencies regard all regulation as good and more as desirable, regardless of costs.[13] Agencies will aim to maximise their size or budget. This can be achieved by exaggerating the social benefits from, say, improved product safety (e.g. the 1968 Act) and ignoring, or under-estimating, the costs of regulation. Usually, regulatory requirements will reflect the least-cost methods of regulation for the licensing authority which might not be least-cost for society. More tests extend the bureaucracy's activities, whilst the costs of these tests are not borne by the regulator but by the regulated or the tax-payer. Furthermore, licence fees provide the regulatory agency with funds to finance inefficiency, labour hoarding and discretionary activities.

2 Protection of the Industry

Some economic models of regulation suggest that it might benefit the Industry (e.g. the regulated) rather than society.[14] Producers can combine to form an interest group aiming to influence Government policy in their favour. They might lobby for tariffs or restrictions on the entry of 'unreliable' firms offering cheaper and hence 'inferior and unsafe' products. In this model, regulation represents an industry buying protection with Government supplying different forms of regulation in return for financial and political support. Furthermore, legislation is attractive to vote-conscious Governments since they can be seen to be 'safeguarding the public'.

3 Intermediate and final outputs

As is typical in the health care sector, confusion exists between inputs, intermediate outputs, and final outputs. For example, there is often a concern with the form of testing rather than the social value of the end output. Regulators and experts will select the 'respectable and safe' methods of regulation and assess 'success' by the extent to which the process is regulated and the number of reports, statutory instruments and licences, rather than the effects on consumer well-being. Here, the usual argument is that consumers (patients) cannot interpret 'complicated' information and should not be allowed to express their attitudes to risk. The validity of this argument can be doubted. Furthermore, committees are likely to be risk averse. If mistakes occur, the amorphous committee is always to blame and no individual is at risk! The extent to which they are subject to incentives, rewards, and penalties for 'good' or 'poor' performance (whatever that might mean) is generally limited. On occasions, the criteria used by independent bodies of experts seem designed to protect themselves as reputable judges and ensure a quiet life! If so, the regulatory arrangements under the 1968 Act may protect administrators as much as, or more than, patients.

4 The 'grass is always greener' and the 'nirvana' fallacies

The impression created by state regulation is that it can improve safety without any other adverse effects and costs, and that in the regulated situation drugs are 'safe'. But regulation is not costless. Firms have to employ staff to prepare their submissions and negotiate with the licensing body. Also, economic models of firm behaviour suggest that regulation might induce producers to use cheaper foreign locations for testing and to invest more in 'me-too' products and less in riskier and more novel drugs. There is no such thing as a 'free lunch': all benefits have to be paid for with scarce resources which have alternative uses. Consequently evidence is required on the direct and indirect costs of the 1968 Act and any resulting benefits. Has safety, quality and efficacy been improved by the Act and, if so, are these benefits more valuable than the costs involved in acquiring them? Here, an official view is that '... no medicines can be regarded as completely safe.

There is always a risk ... of adverse side effects. It is ... impossible for any practicable programme of testing or of evaluation of the testing by supervisory bodies, to offer an absolute safeguard.'[15]

E CONCLUSION: THE NEED TO MONITOR REGULATION

Evidence is obviously a fundamental requirement for any critical appraisal of the 1968 Act. Does the evidence support the critics' claims of substantial costs and dubious benefits? If so, society might wish to consider alternative forms of de-regulation. Or, has the Act made a major contribution to improved patient safety, such that its social benefits greatly exceed any costs? Its supporters also claim that regulation has had no adverse effect on innovation and has resulted in a 'socially desirable' reduction in the 'excessive' number of drugs on the UK market. Further social benefits are claimed in the form of an improvement in the reporting of adverse reactions. In the circumstances, sensible public choices about the extent and form of state regulation require information on the likely costs and benefits of the existing arrangements. For example, the Act has extended testing activities before the launch of a new product. But there is little evidence to enable society to identify the 'best' level of testing. Should the New Chemical Entity (NCE) be administered to rats and beagles for 6, 12, 18 or 24 months; and what is the productivity of each additional period of testing? Unfortunately, the regulatory authorities, if we assume them to be budget maximisers, have every reason to extend the time periods for tests. More tests extend the bureaucracy's activities and the costs of testing are borne by the regulated and the taxpayer! In the meantime, Industry will respond and adapt to regulation. How has the UK Pharmaceutical Industry responded to the 1968 Act and are the results socially desirable?

Part II: Evidence on the Effects of the 1968 Medicines Act

I THE QUESTIONNAIRE DESIGN

1 Aims and methodology

Whilst drug regulation may improve the safety, quality and efficacy of drugs, it uses scarce resources to achieve these goals. There is also the possibility of indirect, unexpected and undesirable effects from regulation. A questionnaire was used to identify and quantify these costs and some of the benefits of the 1968 Act.[16] The questionnaire was divided into four parts (for details, see Appendix A):

(i) A general section designed to obtain information on firms' beliefs about the effects of the 1968 Act—i.e. on patient safety, R & D, exports, quality control, advertising, and the behaviour of the licensing authority.

(ii) A section concerned with eliciting the costs of the 1968 Act, particularly the costs to firms of administering the regulatory system.

(iii) A section requiring precise information about products developed by each firm between 1964 and 1979.[17]

(iv) A section requiring data on each firm's employment, output, exports and R & D spending for the period 1960-79.

Economic models of market structure and firm behaviour were used to predict the likely effects of the objectives and policies of the 1968 Act. These predictions, together with the beliefs of the Industry were tested using both questionnaire and statistical techniques. The result is evidence on the Industry's views of the costs and benefits of the legislation, reinforced where possible with supporting statistical data (e.g. on time scales for drugs; employment changes). Economists, though, are interested in opportunity costs in the form of the sacrifices incurred by doing one thing rather than something else. Such costs are usually measured by prices. However, prices are not always accurate indicators of opportunity costs. Markets might 'fail' to work properly because of imperfections and externalities.[18] For example, under monopoly, prices over-estimate opportunity costs. Also, prices reflect *private* costs incurred by firms, and these might not be an accurate indication of the costs incurred by society (social costs). Furthermore, some costs are difficult to quantify if goods and services are not traded in the market. The expert members of Government advisory committees offer advice for little or no remuneration: such money expenditures are not an accurate measure of the true opportunity costs of the committees (e.g. CSM, CRM). So, this study and the questionnaire results have a lot to say about the *costs* of the 1968 Act. Costs are defined to embrace:

(i) Direct costs: are the resources tied-up in administering regulation trivial or substantial (i.e. in the private and public sectors)?

(ii) Private and social costs: are there any differences in the costs incurred by the Industry and those borne by society?

(iii) Indirect costs in such forms as the effects on development time scales for new drugs, on the rate of innovation and on the location of R & D.

In addition to providing evidence on the costs of the Act, the questionnaire also presents information on its benefits and so contributes to the debate on the social desirability of the legislation (i.e. is it worthwhile?)

2 Sample and response

The main features of our sample and questionnaire response were:

(i) Questionnaires were sent to 25 companies. The sample consisted of major UK and foreign-owned firms, selected by ABPI, together with a set of firms *chosen by the researchers* on a random sample basis.

(ii) The questionnaire was posted to firms in February 1980. There was a follow-up by letter and by telephone, but not by interview. Final responses were received in late September 1980.[19]

(iii) A total of sixteen questionnaires were returned, representing replies from *seventeen* companies (as a result of a merger, one questionnaire was completed for two firms). This gives a 68% response rate, which is an impressive result for a postal questionnaire.

(iv) Not all questions were answered by every respondent and in the case of two companies, the questionnaire was only partially completed.

(v) Some firms did not return the questionnaire because they felt that it was not relevant to their company. Four responses are indicative of the difficulties, especially for small enterprises and foreign firms:

(a) A small firm 'felt that the information required clearly related to the larger companies within the Industry: the decision not to return the questionnaire was therefore a considered one'.

(b) One company maintained that 'we have a small staff dealing with regulatory affairs and, unfortunately, we are unable to dedicate resources to completing the questionnaire'.

(c) A US-owned company replied that 'we could satisfactorily respond to questions related to the FDA but the structure of our organisation is such that we are unable to do so in a way relevant to the UK Medicines Act'.

(d) Another foreign-owned unit explained that its key staff were 'engaged in activities as a result of the Medicines Act' and that it would be 'unfair to ask them to take time off from these important duties. Further, it seems that this study is mainly aimed at British-based companies. Our major research is in the USA and the changes made by the 1968 Medicines Act can only apply in part. I can safely say that the legislation has certainly involved us in increased expenditure within the UK in the areas of registration, data sheet information to doctors and has not enhanced the value of the UK as a research-based country for investment by overseas corporations. I hope you will understand from what I have said that the 1968 Medicines Act is far more of a liability than an asset to this industry, particularly in encouraging foreign investment'.

(vi) Details of the questionnaire and statistical evidence and analysis were circulated to the Industry for comments. As a result, we are confident that the questionnaire evidence and empirical estimates are a reasonably accurate indication of the Industry's views on the 1968 act.

3 Limitations of the questionnaire

The questionnaire evidence reflecting the Industry's views and beliefs is subject to a variety of problems:

(i) Questionnaires encounter problems of bias by the respondent or the researchers. Difficulties also arise in identifying the relevant decision-maker in each company, in holding other things constant, and in quantifying the contribution of different influences. For example, everyone might agree that the 1968 Act has had an effect on R & D, but the relevant question is *how much* of an effect in relation to other causes? We have tried to minimise some of these problems:

(a) *Bias.* Questions are included to check on the consistency of replies and further checks are possible where firms supplied data on employment and the time-scales for developing new drugs—i.e. do their statistics support their questionnaire answers?

(b) *Relevant decision-makers.* Often firms circulated the questionnaire amongst groups of senior managers ranging from regulatory staff to directors.

(c) *Other influences and quantification.* Some questions asked for replies to be ranked in order of importance and 'weighted', whilst others asked for the broad quantitative contribution of the '68 Act—e.g. does it explain everything, about 50% or under 25% of the change?

(ii) Companies might interpret questions in different ways and use different definitions, particularly in an Industry containing multi-nationals and diversified enterprises (e.g. selling costs, capital employed, profitability, testing, development, marketing). One firm explained that its answers were not restricted to the effects of the 1968 Act alone but included the various regulations made under the Act. In this context, its main complaint concerned 'the confusing array of piecemeal legislation'. This is but one example of the ambiguity, misunderstanding and misinterpretation which can arise with both questions and responses, especially with postal questionnaires.

(iii) The counter-factual—i.e. what would have happened in the absence of the 1968 Act? Problems of interpretation arise because in the absence of the 1968 Act, companies would have adjusted to changing social pressures and new technology (e.g. voluntary self-regulation). As a result, firms found it difficult to separate out the impact of the 1968 Act from voluntary advances, the effects of world-wide regulation and the extra costs associated with increased business.

(iv) In some cases, honest and reliable answers would require a substantial management effort, so increasing the attraction of 'guesstimates'. This is more likely with postal questionnaires. Nevertheless, the range of replies from different firms does at least provide a check on the reliability of such guesstimates, as well as indicating a 'best guess' together with the likely upper and lower bounds of the estimates. Some of the variations in the range of replies also reflects the diversity of firms in the sample—e.g. companies with different types of activity and different types of organisation. In these circumstances, a simple rule was used: the more firms supporting a particular response, the more reliable the generalisation. We are most confident about those results which were supported by all the firms responding to the questionnaire.

(v) A major limitation arises from the composition of the sample. The questionnaire was not sent to companies which were in the Industry when the 1968 Act was introduced, but have since left the Industry. Small firms are obvious examples. *By excluding exits due to the 1968 Act, we are likely to under-estimate the effects and quantitative magnitude of the legislation.*

Clearly these limitations need to be borne in mind in examining and interpreting the questionnaire evidence. Nevertheless, checks and safeguards were included in the research. At various points, questions were used to check for the consistency of responses. Elsewhere, statistical data on development times for actual drugs and employment records were used as further checks on a firm's views and beliefs about the effects of the Act (e.g. are the beliefs supported by the data?). And, where data were unavailable (as is often the case, so that statistical tests are not possible) the opinions of firms provide useful insights into behaviour. Thus, we are satisfied that in the circumstances,[20] the results provide a reasonably accurate and reliable analysis of the effects of the 1968 Act. They represent one of the first UK attempts to estimate and quantify the economic effects of regulatory legislation. In addition, the results provide insights into the general behaviour of the Pharmaceutical Industry.

II QUESTIONNAIRE RESULTS

The Effects of the 1968 Act

1 A guide to presentation

The results are presented in the order used in the questionnaire. For guidance, each sub-heading below refers to the relevant section of the questionnaire. A summary of the responses is contained in Appendix A. Commercial confidence prevents the disclosure of individual company replies: hence, the use of aggregates. The evidence is analysed by number of responses, size of firm and ownership. Any relevant differences in the replies are reported. Otherwise, it can be assumed that no significant differences were identified.

2 Characteristics of the questionnaire sample

(See Appendix A, Questionnaire, General Section, questions 1-4)

2.1 The 16 respondents comprised 7 UK and 9 foreign-owned firms, employing a total of 55,147 persons in the UK in 1980. This was almost 75% of employment in the UK Pharmaceutical Industry, so confirming the comprehensive coverage of our sample and the reliability of the results. The main R & D effort of the British companies was located in the UK. For the majority of foreign enterprises, the USA was the main R & D centre.

2.2 On the basis of *employment in the UK,* British firms were larger than the foreign-owned units. The average size of firm in the sample was:

Ownership	*Average employment in the UK*
UK-owned (n = 7)	6,802
Foreign-owned (n = 9)	837
All	3,447

2.3 The sample contained a reasonable mix of large, medium and small firms. The size distribution of firms by employment was:

Employment	*Number of firms*
Over 2,500	5
1,000 - 2,500	6
Under 1,000	5
Total	16

2.4 Only 11 firms provided data on capital employed and these had a labour force of 37,355: some 50% of employment in the Pharmaceutical Industry in 1980. Total capital employed by the 11 firms was £654.7m in 1979, of which UK-owned firms accounted for some 70%. Also, the UK-owned units had more capital *per firm.* But, the foreign-owned companies were more capital-intensive, with substantially more capital *per employee:*

Ownership	*Total Capital (£m)*	*Capital per Firm (£m)*	*Capital per Employee (£m)*
UK-owned firms (n = 6)	465.8	77.6	14,552
Foreign-owned firms (n = 5)	188.9	37.8	35,341
Total	654.7	59.5	17,526

2.5 A comparison of the sample and the Industry characteristics showed that the questionnaire was reasonably representative, although it was dominated by UK-owned firms. Such a bias towards UK enterprises was regarded as acceptable in view of the concern expressed by these firms about the effects of domestic regulatory requirements. Some of the main characteristics of the sample are shown below:

	Characteristics of: *The Sample*	*The UK Industry*
R & D as percentage of sales	10	13.2
Selling costs as percentage of sales	10	10
Percentage of UK-owned firms	44	18
Typical drug:		
Development time (yrs)	8-10	10+
Development cost (1979 prices, £m)	10	20-30

3 General Effects of the 1968 Medicines Act

(See Appendix A, Questionnaire, Section A, questions 1-3)

3.1 Industry and the DHSS claim that the 1968 Act has had many effects, ranging from improved safety to restrictions on advertising. We listed fourteen possible effects. From this extensive list, we asked firms to rank up to *five* in order of importance. In this way, we hoped to identify the *major* effects as seen by Industry. The replies were ranked using two criteria, namely the number of responses and the total points allocated to each of the five rankings. The rankings are shown in Table 3.1.

TABLE 3.1

Rank order		*Major Effects: By number of responses*		*By points*	
1	(Longer development)	iii	(16)	iii	(55)
2	(Less basic R & D)	v	(12)	v	(25)
3	(Fewer new drugs)	iv	(10)	iv	(21)
4	(Restrictions on advertising)	xiv	(9)	vi	(16)
5	(More R & D abroad)	vi	(8)	xiv	(10)
6	(Higher prices)	ii	(6)	ii	(9)
7	(Inefficiency)	vii	(6)	vii	(5)

Note to Table 3.1 Figures in brackets refer to number of responses or total of points allocated to each effect—e.g. 16 firms stated that (iii) was a major effect, with 13 placing it first and 2 placing it second. Similarly (iii) accumulated a total of 55 when the replies were weighted by points (see Questionnaire, A2). The points also show the strength of preferences—note the intensity of preferences for effect (iii). Similar rankings were obtained when the replies were weighted by firm size—e.g. firms accounting for 75% of employment in the sample stated that (iii) was the first ranked effect. Thus, there is strong support for effect (iii), namely longer time scales.

3.2 *There was strong support for the view that as a result of the 1968 Act it takes longer to develop and market new drugs.* The extra time taken varied between 20% and 300% with a median of some 75%. One large company maintained that it now takes three years longer, of which 50% is due to the Act—i.e. a delay of six months at the Clinical Trial Certificate (CTC) stage and twelve months at the Product Licence (PL) stage (the remaining extra time is due to increased sophistication in techniques). Another enterprise believed that the Act has resulted in the 'imposition of 12-24 months of unproductive delay into the development calendar for an NCE'.

3.3 Table 3.1 shows that the Act has also resulted in additional, related effects on R & D activity in the UK:

(a) Fewer new drugs are marketed (e.g. 'less return from innovation: more wasted innovative effort').

(b) There is less basic research and more spent on development. It seems that some 12% to 56% *less* is spent on basic research, with a median of 30% less.

(c) UK firms are now undertaking more clinical R & D abroad. Often this involves Phase I and II clinical trials, with possibly 20% of annual R & D outlays now spent abroad (one British-owned firm declared that 40%-80% of its *clinical* R & D is now spent abroad). Usually, this expenditure is incurred in West Germany, Scandinavia and the USA, although mention was also made of Australia, Belgium, Holland and South America.

(d) There was some evidence of inefficiency in testing. This takes such forms as too much testing, restrictions on innovatory testing as well as ineffective tests (e.g. too early; inappropriate timing; criticisms of pre-CTC tests). The interesting policy question is whether such features of the testing process represent socially-efficient 'solutions' to achieving patient 'safety'. Or, are they least-cost solutions for the regulatory agency (and not necessarily society)?

3.4 In addition to its impact on R & D, firms felt that 'greater restrictions on advertising, information and packaging' (xiv), were a further major effect of the Act. There was also some *limited support* for the Act resulting in higher prices for drugs (ii), but no firm indicated how much higher. For example, one respondent stated that it was 'impossible to calculate since prices are determined not by one factor alone'.

3.5 Whilst Table 3.1 identifies the major effects of the Act and their relative importance, we were also interested in the options which were NOT selected by firms. It should be remembered that we restricted firms to a choice of up to five major effects. In this context, only *two* firms stressed improved patient safety as a major effect of the Act (and they gave it ranks of four and five)! Similarly, little emphasis was given to any loss of international competitiveness, reduced imports of inferior drugs and less copying. Nor did any firm believe that increased productivity in R & D was a major effect of the Act.

3.6 *Thus, Industry believes most strongly that the Act has had a major effect on R & D activity* in the form of longer development times, less innovation, less basic research, more clinical R & D abroad and inefficiency in testing. Every firm recognised that the 1968 Act was not responsible for all the major effects. *Nevertheless, ten firms accounting for 75% of employment in the sample, claimed that the Act explained most of the effects which they had listed* (i.e. 50%-99%).[21] For the whole sample, the median exceeded 50% (i.e. the contribution of the Act). Only one firm believed the effect of the Act had been 'small': it stressed that without the Act, it would still need to carry out all the extra tests required for *overseas* registration, particularly for the USA.

4 Research and Development: trends, time-scales and the costs of drugs

(See Appendix A, Questionnaire, Section A4)

4.1 The sample suggests an Industry in which real R & D spending has risen since the 1968 Act. No firm reported any fall in such spending. Similar numbers of firms felt that the Act was largely or partly responsible, or explained very little of the higher R & D spending. Adjusting the replies by size of firm suggested that the typical outcome was that the Act *partly* explained the increased R & D spending (i.e. 25%-50% explanation). *Firms were unanimous that regulation in the rest of the world together with technical progress had also effected their UK R & D expenditure.* In which case, overseas regulation (some of which might be due to the UK example?) and technology might explain up to 75% of higher R & D spending.

4.2 Since 1968, the major sources of higher real R & D spending have been (ranked by number of respondents, as shown in brackets):

(a) Toxicology (n = 10), where increases in spending were 100%-370% with a median of 300%.

(b) Clinical studies, trials and testing (n = 7), with increases ranging from 75% to 400%.

(c) Drug metabolism (n = 3), with one firm reporting a 300% increase in spending.

(d) Biology (n = 1), with one case of an increase of 400%.

(e) Increased sophistication (n = 1), such as automation and the greater use of computers for information retrieval. In one firm the result has been a 200% increase in R & D spending.

(f) Higher personnel costs (n = 1). For one firm, personnel costs are now 50% of the budget, compared with about 30% in 1969.

(g) General consumables (n = 1), with one example of a 50% increase.

4.3 The items of UK R & D spending which have increased *mostly because of technical progress and the increasing complexity of R & D work* have been:

(a) Drug metabolism (n = 4).

(b) Increased use of automation, computers and complex instruments (n = 4).

(c) Toxicology (n = 3).

(d) Other items mentioned included analytical and basic research, biology, clinical pathology and pharmacology, as well as an increased use of animals and radio-chemicals.

4.4 Where outside research agencies and laboratories are used, firms allocated 0.5%-80% of their UK R & D budget on such work: the median was 4%. For the largest firms in the sample, the figure ranged from 0.5% to 6%. There was some tentative evidence that the percentage of outside research contracting has risen in the last ten years, with the 1968 Act accounting for, say, 50% of the increase (the responses were weighted by firm size, and influenced by one large unit).

Using a median figure of 4% the UK industry spent about £9m on sub-contract R & D in 1979 (industry R & D of £224m). Most sub-contract R & D is toxicity testing for regulatory purposes and estimates suggest that 30% is due to the 1968 Act. *This results in an estimated annual expenditure of £2.7m on sub-contract R & D required to meet the Act.*

4.5 (a) *The time scale and costs for developing a typical drug.* Firms were asked for data on the time and cost required to develop a typical drug in 1979-80 compared with a situation without the 1968 Act. This question was designed to obtain information on the quantitative impact of the Act, as well as providing a check on responses elsewhere in the questionnaire. Almost all firms were able to answer the questions about time scale, but considerably fewer provided cost data, especially in the absence of the 1968 Act. Clearly, generalisations show broad orders of magnitude with the actual details depending on a firm's financial position (e.g. profitability), its size, its R & D policy and the complexity of its drugs. The median answers to the questions on time and costs are shown in Table 4.1:

TABLE 4.1 Time and Costs

	Time (yrs)		*Total cost (£m 1979 prices)*	
Development Stage	*Now*	*Without 1968 Act*	*Now*	*Without 1968 Act*
(1) Patenting of NCE to CTC	4	2-4	2.2-2.5	1.5
(2) Patenting of NCE to market launch	8-10	6	9.5	7-8

Note: Time scales are based on n = 14; cost data are based on n = 7 for Now and n = 6 for Without 1968 Act. See Appendix A for further details.

(b) Table 4.1 shows that a 'typical' drug requires a total of 8-10 years from patenting a NCE to market launch, with some 40%-50% of the time used up to the CTC stage. Such figures conceal a diversity of experience, with total development times ranging from 5 years to 15 years. Similarly, the total cost of a 'typical' drug is about £10m (1979 prices), with some 25% of the expenditure incurred up to the CTC stage. Once again, the median is derived from a set of drugs where total costs range from £1.5m to some £30m.

(c) *Almost all firms claimed that without the 1968 Act, drugs would be developed FASTER.* Only *one* firm stated that there would be no change. *For a 'typical' drug, in the absence of the Act, the median development time was estimated at 6 years, giving a saving of 2-4 years,* including a saving of one year up to the CTC stage. This result confirms the findings on the general effects of the 1968 Act, where the replies gave a typical increase in time scales of 75%, with over half of the increase attributable to the Act (Table 3.1 and Appendix A, Section A, question 1). Table 4.1 provides direct evidence assuming no Act, and the orders of magnitude are consistent with the replies given to the earlier questions on the effects of the Act.

(d) The cost data were less reliable, based on only six responses. Without the 1968 Act, three firms stated that there would be no reduction in total costs. For the remaining three firms, the median cost saving was estimated at £2m per drug (1979 prices).[22]

4.6 (a) *Significantly, all the British-owned firms reported a decline in the proportion of their R & D undertaken in the UK. The median figure declined from 100% in 1968 to 80% in 1979.* Such results are also consistent with the findings on the general effects of the 1968 Act (Table 3.1). In contrast, none of the foreign-owned firms reported any decline: their percentages were either unchanged or higher.

(b) For firms in the sample, there was some tentative evidence of an *increase* in their UK R & D outlays as a percentage of UK sales. The median rose from 7.5% in 1968 to 10% in 1979.[23]

4.7 Firms accounting for about 50% of employment within the sample claimed that the 1968 Act had biased their research programmes towards certain types of drugs. Such a response can be taken as reasonably reliable, since any Industry 'bias' against the Act is likely to have resulted in a higher percentage of firms claiming an effect on their R & D programmes. Where the Act has affected R & D programmes, the bias seems to have been towards:

(a) The development of drugs for major diseases and for larger markets. It was explained that R & D costs and time scales mean that only products with a widespread use are worthwhile (n = 4).

(b) Derivative research at the expense of basic innovatory research (n = 1).

(c) Compounds with acute pharmacological activity which can be demonstrated in healthy volunteers (n = 1).

4.8 The majority of firms claimed that they would enter UK-based R & D today. Indeed, the point was made that most other countries also present disadvantages, either in terms of costs or registration requirements. Only three firms (two UK-owned), declared that they would not, giving as their reasons:

(a) 'The investment would be too great and too risky' (n = 1).

(b) 'Inconsistency of Government policy; too much preliminary toxicology before clinical evaluation commences; increasing unionisation' (n = 1).

(c) 'Without an underlying established business, we could not justify the level of expense against the uncertainty' (n = 1).

4.9 Thus, the questionnaire evidence confirms that the Act has had major effects on R & D activity:

(a) It partly accounts for higher R & D spending (say 25%-50%), and for the greater use of outside research agencies.

(b) For British companies, there is evidence of a substantial reduction in the proportion of R & D work undertaken in the UK.

(c) The Act has resulted in longer development times, possibly an extra 2-4 years for a typical drug.

5 Exports: trends, prices and profitability

(Appendix A, Questionnaire, Section A5)

5.1 Exports in real terms have increased. For most firms, the volume of exports has risen since the 1968 Act. No firm reported a decline. Firms were unanimous that the 1968 Act explained 'very little' (under 25%) of any increase. One commented that the Act 'had caused some decrease, but this has been more than compensated for by other factors'. In other words, some of these results might be consistent with the Act having adverse effects on exports (see below).

5.2 Export prices are either *higher* or the same as the UK prices of drugs. In general, export prices were affected by:

(a) The usually higher costs and risks of overseas business (n = 6).

(b) The extent of overseas competition (usually more; n = 3).

(c) The 1968 Act. Two firms claimed that the Act has raised selling costs. One company stated that the Act has 'pushed up costs, making products less competitive in marginal markets'.

(d) Other influences, such as adverse currency movements, UK Government intervention, extended distribution chains and local restrictions on price increases.

5.3 Exports are usually as profitable or more profitable than home sales. The *higher* profitability of exports was explained by:

(a) The presence of UK price restrictions. This explanation was given most frequently (n = 6), two firms stressing that 'the PPRS has held UK prices down'. Such price restrictions are a further aspect of regulation, but they were outside our study of the 1968 Act.

(b) The absence of UK regulatory requirements, although only one firm mentioned this as an explanation.

(c) Other influences included higher prices and lower fixed costs, as well as attention to market factors, product mix and scale economies (n = 2).

5.4 Firms were unanimous that they had *not* established local (foreign) processing facilities as a result of the 1968 Act.

5.5 In total, the replies provided some insights into the Industry's export performance and its relative profitability. The responses are consistent with the beliefs about the general impact of the 1968 Act, where loss of international competitiveness was not regarded as a major effect (Table 3.1). However, it might be that the effects of the 1968 Act on exports are more indirect through, say, its impact on the UK as a competitive centre for R & D. In this context, one firm felt that a specific and relevant question had been omitted from the questionnaire: how do the costs of drugs from the UK and other countries compare and what effect does this have on trading? Its reply was that 'UK costs are generally higher—and this reflects directly on the costs of implementing the Act and its requirements. In markets where generic ordering or product substitution are practised, business can only be gained by paring margins. There comes a time when prices cannot be matched and products have to be withdrawn from the market'.

Undoubtedly, export pricing and profitability[24] is a complex subject and its complexity might explain why firms gave little emphasis to the loss of international competitiveness. One firm explained that '... there undoubtedly had been a loss of competitiveness of our products in overseas markets as a result of the increased costs which have arisen from excessive regulation, but this has been counteracted by price controls which have kept our products competitive, but only at the expense of profit margins'. In export markets, foreign authorities often insist that the local price equates to the price in the market of origin. Thus, 'in the case of the UK where our domestic prices have been artificially depressed by the PPRS to the extent that British drugs have been just about the cheapest in the world, the consequent depression of

export prices has been to keep them down to the serious disadvantage of profits'.

6 Quality Control: trends and voluntary behaviour

(Appendix A, Questionnaire, Section A6)

6.1 We were interested in the effects of the Act on quality control and how firms might have behaved in the absence of the legislation. In 1968, expenditure on quality control ranged from 0.3% to 10.6% of total sales, with a median of 2% to 2.7%. The UK-owned firms had the highest percentages. By 1979, the equivalent range was 0.5% to 7.3% and a median of 1.5%. Interestingly, for 1968-79, all the foreign-owned firms providing data reported a *rise* in expenditure on quality control as a percentage of sales. Of course, between 1968 and 1979, total sales have risen so that percentages can be misleading indicators of expenditure on quality control. Also, technical progress has occurred, so that quality control laboratories are now more capital-intensive than in 1968 (i.e. higher labour productivity). Fortunately, a limited number of firms (n = 5) provided time-series data on output, so enabling a more accurate analysis. For this limited number, it seems that expenditure on quality control as a percentage of sales was relatively unchanged between 1968 and 1979, averaging 1.36% and 1.33%, respectively. But the *magnitude* of the expenditure was different, as shown in Table 6.1.

TABLE 6.1
Expenditure on Quality Control £m 1975 prices

Item	*1968*	*1978*
Expenditure on quality control	1.326	3.725
Value of sales	97.3	283.5
Quality control as % of sales	1.36	1.31

Note: Expenditure figures are in constant prices, 1975 = 100, using the price index for Pharmaceutical Preparations, *Annual Abstract of Statistics*, HMSO, London. At the time of the study (1980) constant price data were only available to 1978: hence the difference between the Table based on 1968-78 and the text based on 1968-79. The sample was based on n = 4 for 1968 and n = 5 for 1978.

For the same number of firms (n = 4), *real* expenditure on quality control increased by 262% between 1968 and 1978. But during the same period, real sales of the firms (n = 4) also rose by almost the same percentage. *In other words, there is evidence of a positive relationship between real sales and quality control expenditure* (both variables move in the same direction, rising together). Expressed in 1979 prices, a sample of five firms accounting for over £450m of sales, spent some £6m on quality control in 1979. In some cases, annual expenditure was £1.8m to £2m per firm. *If such results are typical, then the Industry as a whole might have spent some £26.5m on quality control in 1979.*[25] To what extent are such expenditures due to the 1968 Act?

6.2 Firms accounting for over 60% of employment in the sample stated that the Act had improved quality control in manufacturing. Attempts to quantify the *extra* capital and production costs of improved quality control were less successful, some firms maintaining that it was 'impossible to say'. However, the figures given (n = 7) ranged from £118,000-£150,000 per annum to sums of £5m-£7m (1979 prices). In at least one case, it was stressed that only a small part of the increased expenditure was due to the 1968 Act. There are obvious difficulties in interpreting these answers. Firms might have confused capital and production costs; it might be difficult to differentiate between the extra costs of improved quality control and those resulting from increased volume; and some firms might have shown gross rather than net expenditures (e.g. they might have included the costs of a completely new plant even though the expenditure would have been incurred without the Act). In addition, there are difficulties of definition. Quality control is a complex function involving control and analytical departments as well as production, engineering and maintenance. Nevertheless, and bearing in mind these qualifications, one firm provided a detailed analysis of its extra outlays on quality control and this is reproduced in Table 6.2 below.

TABLE 6.2
The Quality Control Costs of the 1968 Act: One Firm's Experience £, 1976 prices

Item	*Capital Costs (One-off)*	*Annual Costs: Definite*	*Probable*
a. Fixed assets expenditure to bring to Medicines Act standards	1,204,000		
b. Quality assurance in factory		50,000	
c. Documentation in Quality Control		8,000	
d. Additional variable costs:			
Cleaning		30,000	10,000
Wastage		30,000	
Total costs	1,204,000	118,000	10,000

Note: Items are for quality control only and refer to costs solely due to the Act which would *not* otherwise have been incurred.

The figures in Table 6.2 can be used to provide a guesstimate of the extra costs incurred by the quality requirements of the 1968 Act. Assume that the firm at Table 6.2 is 'typical' and that its experience can be 'grossed-up' for the whole Industry and expressed in 1979 prices. *Using such heroic assumptions, the result is an estimated additional expenditure of £6.2m per annum (1979 prices) due to the quality control requirements of the Act:* a figure which represents about 23% of the Industry's estimated annual expenditure on quality control (see below). Similarly, the quality control requirements of the Act might have resulted in extra capital costs of over £63m since 1968 (1979 prices).[26]

6.3 Firms were almost equally divided on the effect of the quality changes on patient safety. Enterprises accounting for some 50% of employment in the sample did *not* believe that the quality changes due to the Act had improved patient safety: the remainder felt that patient safety

had been improved. In this context, almost all firms maintained that they would have introduced additional quality controls without the 1968 Act. The general view was that the costs of such voluntary improvements in quality control would have been the *same* or *lower* than the outlays required for the 1968 Act. *This suggests that a voluntary system would have resulted in lower costs for quality control.* At the same time, it was claimed that voluntary quality control would result in *unchanged* patient safety compared with the current situation: *no firm believed that patient safety would be lower.*

6.4 If a voluntary system would result in *unchanged* patient safety and *lower* costs for quality control, what is the possible magnitude of the cost savings? Only half of the sample believed that quality control costs would be lower under a voluntary system. *On this basis, there might be savings on quality control of some £3m per annum (1979 prices)* without the Act.[27] Such estimates are no more than tentative. Moreover, in assessing the quality control effects of the Act on both patient safety and costs, it must be stressed that the replies are based on existing companies. The Act might have introduced quality improvements and higher costs for the fringe and marginal companies, rather than the major enterprises; but companies which have left the Industry were not included in the sample. In other words, the results reported in the questionnaire could be under-estimates of the effects of the Act on patient safety and costs.

7 Advertising: expenditure and results

(Appendix A, Questionnaire, Section A7)

7.1 For firms in the sample, advertising and selling expenditures as a percentage of total sales varied between 5% and 19% for most of the period. Answers to this question were obviously dependent on accounting systems and the definition of selling costs, with some firms excluding packaging and merchandising items. Even so, generalisations were possible. For the majority of firms, advertising and selling as a percentage of sales fell slightly between 1968 and 1979, the median figure declining from 11% to 10%.

7.2 The majority of firms stated that the 1968 Act had resulted in changes in their advertising, information, packaging and merchandising policies. The major changes were given as:

(a) Data sheets (n = 7).

(b) Controls on advertising and promotion, the provision of warnings and the employment of staff to monitor advertising policies (n = 5).

(c) Labelling (n = 4).

(d) Child-proof packs and foil packs (n = 3).

(e) More legal and scientific input and higher costs due to the administrative burden (n = 1).

7.3 In general, the changes due to the 1968 Act were believed to have resulted in *higher* selling costs for firms: such higher costs might have been experienced by some 50% of the Industry.[28] However, only two respondents gave specific figures ranging from a 1%-10% increase, with another suggesting only a 'marginal increase'; and one firm estimated the extra costs of labelling packs at a once-and-for-all sum of £20,000 (1976 prices). The overwhelming majority of firms claimed that the changes due to the 1968 Act had resulted in the *same* volume of sales: no firm reported an increase. One enterprise was unable to give an answer since 'sales had risen due to the withdrawal of rivals or changes in their claims but there had been sales losses due to regulatory requirements'.

7.4 In view of the stated objectives, it is not surprising that the 1968 Act has changed firm advertising behaviour. Such changes have raised advertising costs for a *given* volume of sales—i.e. to *firms,* they are inefficient since higher costs have to be incurred for the same business. Society might take a different view and regard such changes as worth-while. However, for these changes to be socially beneficial, evidence is required on the magnitude of their costs and benefits. From the viewpoint of the costs imposed on firms' *advertising* budgets, the magnitude of the change seems to be relatively small, say, an increase of 1% in selling costs. *For the Industry as a whole, selling costs might be 10% of sales, say, some £200m in 1979.* Assume that the Act has affected selling costs in half of the Industry and, where affected, such costs have risen by 1%. *On this basis, the Act might have raised the Industry's selling costs by about £1m in 1979.*

8 The Licensing Authority: applications and documentation

(Appendix A, Questionnaire, Section A8)

8.1 In view of the Industry's complaints of 'excessive bureaucracy', it was necessary to obtain information on firms' experiences with applications for licences. How quickly does the regulatory agency deal with applications? *Typically, the licensing authority takes some 7½ months to handle an application for a CTC and 10-12 months for a Product Licence.* These are median figures and they embraced a range of 4-18 months for CTC and 3-20 months for PL applications.

8.2 Almost all firms agreed that over the last ten years the time taken by the licensing authority to handle applications for both CTCs and PLs had *increased.* The main reasons for the increase were ranked by number of responses and their priority. The results in order of importance were:

(a) First, the shortage of qualified licensing authority staff (n = 15).

(b) Second, increased regulatory requirements (n = 15).

(c) Third, the greater complexity of technology and hence more complex applications (n = 15).

(d) Fourth, increased number of applications to be handled by the licensing authority (n = 12).

(e) Fifth, a greater concern with public safety (n = 8).

It is perhaps noteworthy that three of the top four reasons given refer to regulatory requirements and the performance of the licensing authority. Generally, firms felt that the single most important factor they listed 'largely' explained the increased time. On this basis, the shortage of qualified licensing authority staff and increased regulatory requirements[29] were the predominant causes of the greater handling time. Other possible explanations received little support. Few firms felt that the increased application time was due to their greater willingness to appeal against licensing authority decisions; and no firm referred to its failure to reply to correspondence from the authority! There was also a mention of 'increasing bureaucracy' and of the 'legal framework providing less opportunity for the informal resolution of problems'.[30]

8.3 Two firms had experienced licensing authority refusals to award a CTC and seven enterprises had been refused PLs. If such experience is typical for the Industry, it means that firms accounting for some 20% of total employment have been refused CTCs, and for PLs the corresponding figure is about 30%. Within our questionnaire, most of the firms experiencing a refusal were foreign-owned. Typically, amongst the firms experiencing refusals, some 3%-8% of applications had been rejected, usually for the following reasons:

(a) Withdrawn (n = 5). This seems a strange explanation for a rejection. Presumably, firms preferred to withdraw applications rather than receive a formal rejection.

(b) Failed to conform to testing and documentation requirements, or additional data required (n = 4).

(c) Considered to be unsafe (n = 2).

8.4 Most firms have withdrawn an application to the licensing authority. The major reasons given for withdrawal were:

(a) Extra data and testing required (n = 7). In some cases (n = 3), such extra requirements meant that the product ceased to be commercially viable.

(b) Adverse reactions in trials (e.g. toxic; n = 3).

(c) CSM believed product to be ineffective (n = 1).

(d) It became 'clear that the CSM would not approve in the current climate of medical-public opinion' (n = 1).

8.5 Most firms have delayed the marketing of a new drug *after* receiving a Product Licence. Such delays occurred because of:

(a) Commercial reasons (n = 7), including a re-assessment leading to the judgement that the product was 'non-viable'.

(b) Aiming for overseas sales (n = 2).

(c) Production and supply problems (n = 2).

(d) Inappropriate time of the year for launch (n = 1).

(e) Further studies created doubts about the product (n = 1).

8.6 The median length of documents submitted to the DHSS for a CTC and a PL are shown in Table 8.1. For a NCE, a CTC involves 1600 pages of documentation, although the range varied from 600 to 3000 pages. Similarly, for a PL about 2500 pages of documentation are submitted, with the range varying from 300 to 5000 pages. Some 18 to 20 copies of each document might be submitted. Not surprisingly, the submissions for non-NCEs are considerably less.

TABLE 8.1
Documentation

Submission for:	*NCE (pages)*	*Non-NCE (pages)*
(a) CTC	1600	176
(b) PL	2500	200-250

8.7 Firms were unanimous that the number of pages of documentation submitted for CTCs and PLs has *increased* since licensing was enforced in 1971. The median increase in the number of pages was 200%, but this embraced a massive range of variation from 10% to 1,000%!

8.8 Five firms, accounting for 70% of employment in the sample, felt that the DHSS was faster than other nations at handling licensing applications. However, three of the five qualified their answers:

(a) Two stressed that the DHSS was *slower* than other nations with CTC applications.

(b) One explained that the DHSS was faster than the FDA, Canada, Scandinavia and Australia, but slower than Eire.

8.9 Ten firms believed that there were other nations faster than the DHSS at handling applications. Those mentioned as faster included:

(a) Eire (n = 8), which might be faster by 2-3 months.

(b) Most European nations (n = 6), especially Belgium, France, Netherlands and West Germany. One company claimed that most EEC nations respond to marketing applications within four months (cf UK).

(c) The UK is the 'slowest in the world in handling CTC applications' (n = 3). It was claimed that a number of nations handle CTC applications in 30 days or less (e.g. Belgium, France, Holland, Eire, West Germany and USA).

However, the list of 'faster' nations is subject to major qualifications. Some apparently fast nations lack a significant regulatory machinery and rely upon prior marketing approval in a more regulated country (i.e. they are 'free riding'). Others do not *evaluate* submissions in the same way as the UK (e.g. some nations handling CTC applications in 30

days or less). Nor should target and nominal evaluation periods be confused with the time *actually* taken to evaluate applications. For example, European countries pay lip service to the EEC 120 day statutory time limit but, to quote one firm, '... in practice, approval always takes longer simply because all countries stop the clock when they ask questions'.

8.10 This section has provided evidence on the 'performance' of the UK regulatory agency:

(a) The licensing authority takes 7½-11½ months (say, 9½ months) to handle CTC applications and 10-12 months (say, 11 months) for PLs: *a total of over 20 months,* all of which adds to the time period from patenting to market launch.

(b) The time taken by the licensing authority to handle applications has *increased* over the last 10 years. Industry believes that a shortage of qualified licensing authority staff explains much of this increase. One firm estimated that a submission was under professional scrutiny on only about *20 days*!

(c) There are other nations which are *faster* at handling licensing applications, *particularly at the CTC stage.*[71]

(d) Applications for a CTC and PL for a NCE might involve the submission of over *4,000* pages of documentation: these represent considerable volumes by any standard (e.g. *Roget's Thesaurus,* Penguin, 1966, 712pp: J.S. Mill, *Principles of Political Economy,* Longmans, 1883, 591pp: J.D. Scott, *Vickers: A History,* Weidenfeld and Nicolson, 1962, *416pp*). Obviously, such voluminous documents are time-consuming, both to prepare and to digest. And it must be remembered that the 4,000+ pages of documentation relates to *one* product.

(e) In assessing the performance of the licensing authority and its contribution to delays, some allowance has to be made for the fact that firms often withdraw applications (with their effect on the use of the licensing authority's available staff) and delay the marketing of a new drug after receiving a PL. But with company-induced delays, the costs are borne by those responsible for the decision.

The fact that other nations are faster at handling licence applications confirms that *alternative forms of regulation are available.* For policy-makers, the relevant questions concern the costs of these alternatives and their likely benefits. Economists can contribute to the policy debate by estimating and critically assessing the costs of achieving current objectives (e.g. are there less costly alternatives?), as well as by questioning whether these objectives are worthwhile. At least three issues are involved. *First,* what are the costs of the faster regulatory systems: are they faster than the UK system because they are costlier and have more resources available (i.e. for processing applications)? *Second,* do faster nations have more 'productive' licensing authorities: if so, why are they more productive? *Third,* do the faster nations provide 'less' regulation than the UK? And, if faster nations have cheaper systems involving less regulation than the UK, what are the likely effects on patient safety: is there any observable reduction in safety (and if so, how much)?

Our questionnaire results can contribute to this policy debate by providing evidence on *some* of the possible implications of alternative regulatory systems. For example, if the UK were to handle applications as quickly as is reputed to be the case in some other nations—say, 30 days for a CTC and 4 months for a PL—the total time for handling applications would be *5 months,* compared with a *current average of 20½ months!* Thus, if the UK became a 'fast' regulatory nation, there could be *time savings of at least 15½ months* for a typical drug (i.e. due to handling licensing applications more quickly—the numbers are consistent with answers given elsewhere in the questionnaire). Further time savings might occur if there were corresponding reductions in the regulatory requirements for testing, etc., although such time savings are unlikely to be costless. It is recognised that international comparisons raise enormous *ceteris paribus* problems.[31] Regulatory agencies might be pursuing various objectives, so that confusions can arise if different performance criteria are used. For example, speed of handling applications does not necessarily imply 'proper' evaluation. In this context, it has to be stressed that costs and benefits are subjective, with each nation having its own valuation of costs and benefits (tastes and preferences differ between societies). Nevertheless, the potential time savings from adopting the faster nations' approach appear sufficiently great to justify a critical appraisal of the existing UK regulatory system. *Is the UK buying 'too much' regulation (i.e. over insurance)?*

9 The Likely Effects from the Abolition of the 1968 Medicines Act: what would happen?

(Appendix A, Questionnaire, Section A9)

9.1 In view of Industry's objections to the 1968 Act, we wished to explore how firms might respond to its abolition. The answers provide insights into the possible implications of voluntary self-regulation, as well as acting as a check on the consistency of replies to other questions. Firms were asked how *they* would respond to the abolition of the 1968 Act. Their major replies ranked by number of responses and their relative importance were:

(a) First, more new drugs would be marketed (including new formulations and presentations).

(b) Second, there would be less R & D overseas and more in the UK.

(c) Third, basic research would *increase.* No firm stated that it would reduce basic research, whilst seven maintained that it would remain unchanged and four major employers stated there would be a rise.

(d) Fourth, there would be changes in development work. Seven firms believed that it would remain the same, two that it would rise and three stated that there would be a fall. In the absence of magnitudes, it is not possible to assess the effect on the *Industry's* total development effort.

(e) Fifth, there would be *less* testing (e.g. less development testing).

(f) Sixth, different types of testing would take place.[32] Firms preferred the earlier use of human trials, the later use of expensive animal studies, specifically-tailored toxicology testing, a more flexible approach and less defensive work.

This is obviously a broad question and raises doubts about the 'counter factual' implicit in the responses (i.e. what would be the alternative to the 1968 Act?). Nevertheless, the replies are comparable and consistent with those relating to the major effects of the 1968 Act, particularly on R & D activity (see Table 3.1). In addition, some of the options which received little or no support are worth mentioning. No firm stated that the price of drugs would fall;[33] two firms would undertake more advertising and only three firms declared that they would reduce employment, particularly of registration, testing and quality control staff.

9.2 (a) If the 1968 Act were abolished, the majority of firms would, in general terms, retain all or *most* types of testing. However, there were qualifications. For example, all tests would be retained but 'to a lesser degree' or there would be 'changes in the priority and ordering of tests'.

(b) Five firms declared that if the Act were abolished, they would not *abandon* any tests. However, a further five companies did specify tests which they would wish to abandon and these included:

(i) Abandoning extensive toxicity and safety clearance prior to early clinical trials.

(ii) Formal LD50.

(iii) Carcinogenicity studies 'except in certain special circumstances'.

(iv) 100 patient year clinical studies; but long-term clinical safety studies would continue to be performed.

(c) The overwhelming majority of firms would prefer to *postpone* some testing until later in the development process. These included:

(i) Fertility tests (n = 6).

(ii) Long-term testing—e.g. toxicity; animal studies; carcinogenicity, with postponement to the post-CTC stage (n = 6).

(iii) Some detailed chemical and pharmacy tests (n = 4).

(iv) Drug interaction studies (n = 1).

(v) Basic pattern unchanged, but at a commercial level (n = 1).

9.3 *Abolition of the 1968 Act was expected to result in a fall in the costs of testing.* No firm expected costs to rise, some expected no change and the majority predicted a fall. Predictions of lower testing costs and a general desire to postpone some tests suggests that Industry regards the current testing requirements as *inefficient.*

9.4 There was some support for the view that patient safety has improved as a result of the 1968 Act, although in some instances, the improvement was only 'marginal'. Usually, any improvement was explained in terms of the Act 'protecting patients from companies with inadequate facilities for fully evaluating the safety of their products'; or, it has 'eliminated the unsafe products of some companies' and enforced 'minimum acceptable levels of testing on less reputable companies' (n = 5: see also 9.5 and 9.6 below).

9.5 Firms accounting for about 45% of employment in the sample claimed that, from the *viewpoint of their company,* the Act has *not* had any beneficial effects on patients. Those firms which felt that patients have benefited gave the following reasons:

(a) Patients have been protected from inferior drugs, including imports.[34] Also, higher standards of safety have been introduced. It was, however, pointed out that 'good companies were already at these standards' (n = 6).

(b) The psychological feeling of Government protection (n = 1).

9.6 Firms were unanimous that the Act has had harmful effects on patients *through delays in the introduction of new drugs.* Mention was also made of the Act reducing incentives for R & D on low incidence diseases and rare conditions (n = 3); and of higher development costs and delays 'paid for by taxpayers and patients' (n = 1). Also, it was suggested that the Act might have 'induced false confidence in the general public' (n = 1) and that some patients might have been 'frightened by CSM reports' (n = 1)!

9.7 If the 1968 Act were abolished, Industry would:

(a) Postpone some testing

(b) Experience a fall in testing costs.

(c) Market more new drugs.

Would society regard such changes as beneficial? Presumably, total abolition might lead to the re-entry of allegedly 'inferior drugs, cowboys and priates' (competition?), with possible adverse effects on patient safety and incentives to invest in R & D. Once again, policy-makers have to choose. *Trade-offs between costs, risks and benefits cannot be avoided and there are no costless solutions.* In the circumstances, and in view of the questions on the effects of abolishing the 1968 Act, we asked firms about future policy. Would they prefer the Act to be retained, modified or abolished?

10 Future Policy: should the Act be abolished?
(Appendix A, Questionnaire, Section A10)

10.1 *Firms were unanimous in preferring modifications to the 1968 Act.* Not one respondent argued for the abolition of the Act or retention in its present form. Firms explained their preferences for modifications:

(a) All firms felt that the Act was too bureaucratic.

(b) Substantial numbers felt that the Act has had net adverse effects on the Industry (n = 13).

(c) Firms accounting for almost 90% of employment in the sample believed that the Act has had net adverse effects on *patients* (n = 11).

10.2 The major modifications preferred by firms, in order of importance were:

(a) First, more flexibility in general and, in particular, a reform of the CTC system. Once again, the existing CTC procedure attracted considerable criticism—e.g. 'there should be fewer demands, earlier clinical studies with fewer data requirements, and less restrictions on first administration to patients' (n = 12).

(b) Second, fewer delays and a speedier review of licensing applications—e.g. 'time limits should be introduced for handling applications, so that a firm is allowed to proceed unless it hears from the DHSS within a specified time, say three months after the initial application' (n = 6).

(c) Third, less bureaucracy (n = 3).

(d) Other proposals included the 'removal of advertising regulations' (n = 1) and 'encouragement towards easing the costs of developing drugs for rare diseases' (n = 1).

10.3 Industry's view is that the 1968 Act should be *modified.* Firms would prefer greater flexibility and a faster system for handling licence applications. *Emphasis was placed upon the need to improve the existing CTC procedure.* In other words, Industry would prefer some de-regulation, rather than complete abolition. Interestingly, no firm wanted the Act to be abolished, which was a surprising result in view of the massive criticisms of regulation. This might be explained by the continued existence of international regulatory requirements, so that abolition is viewed as 'unrealistic'.[35] In which case, the preference for modifications can be viewed as a search for changes which will improve the performance of the UK Industry with little, if any, adverse effect on patient safety. However, modifications are not costless. For example, bureaucrats might argue that some of these proposals require more staff and the resulting costs might then be imposed on the Industry in the form of an increased levy!

III QUESTIONNAIRE RESULTS

The Life Cycle in Drug Development: Time Lags Between Synthesis and Marketing of NCEs

1 The need for data[36]

Part of the questionnaire asked firms for data on key dates in the development of NCEs for humans tested or marketed during the period 1964-79 (See Appendix A, Section C). By requesting data for a 15 year period both before and after the 1968 Act, it was hoped that this 'before and after' study would produce more accurate information on:

(a) The life cycle of a NCE.

(b) Delays caused by the regulatory authorities, particularly at the CTC and Product Licence stages, and hence the effects of the 1968 Act.

(c) Delays between regulatory approval and first marketing.

(d) The general effects of technical progress on time scales—e.g. are drugs now taking longer to develop?

(e) The reliability of some of the generalisations in the questionnaire responses.

2 Methodology

Firms were asked to select *five NCEs* on the following basis:

(a) The third and eleventh items in the alphabetical list of their products, as listed in the ABPIs Data Sheet Compendium (i.e. a random selection determined by the researchers).

(b) One pre-1968 product and one from the period 1974-79.

(c) One other product selected by the firm.

For each product, firms were asked to provide various dates ranging from chemical synthesis to applications for a CTC and a Product Licence and the date of marketing in the UK. The detailed data requirements are described in Section C of the Questionnaire which can be found in Appendix A.

3 Response

Eleven firms provided data with varying degrees of detail. In terms of employment, the 11 represented almost 85 per cent of our *sample,* and they accounted for over 60 per cent of the *Industry.* Data were provided on 47 products, with starting dates for chemical synthesis ranging from 1958 to 1974. However, only limited information was available for some NCEs. For example, it was possible to estimate total development time scales for 39 products: hence the variations in the size of the sample.

4 Some limitations of the results

There are a number of limitations and qualifications which need to be recognised when interpreting the results:

(a) The definition of the life cycle. It is not always possible to identify the starting date in the development of a new product. We have selected some clearly-defined points, namely, the dates of chemical synthesis and patenting. The end point in the development cycle raises similar problems, especially where product development is a continuous process. For our purposes, we have assumed that the development cycle is completed with the first marketing in the UK.

(b) The sample contains drugs of different types and complexities.

(c) Differences in development cycles might reflect variations in R & D expenditures. If there are trade-offs between time and cost, then faster development might reflect greater R & D expenditures.[37] In other words, when analysing data on development time scales, problems arise in taking account of other relevant influences (i.e. all things are not equal).

(d) At least one firm explained that it had been unable to select products on a random sample basis as requested. Apparently the number of new NCEs within its present product range was 'very limited', with only one major addition during the previous 10 years.

5 The empirical results: time lags before and after the Act

5.1 The major features of the sample are outlined in Table III.1 below. For all products for which data were provided, the average time from chemical synthesis to first marketing in the UK was 8 years, with a shorter time period of 7 years 1 month from patenting to marketing. Similarly, the average periods for handling CTC and Product Licence applications were 5.4 months and 6.9 months, respectively. As can be seen from Table III.1, these averages conceal a wide range of time scales. A graph of the relationship between starting date (chemical synthesis) and total development time showed an almost perfect scatter!

5.2 Some indication of the possible impact of the 1968 Act can be obtained by considering time scales for products developed *before* and *after* the introduction of the legislation. Table III.2 shows the data for drugs which were started in the period 1958-65 and marketed by 1968-69—i.e. *before* the impact of the Act (n = 12 products). Typical time scales are shown for the major development milestones, within a total development time period of a little more than 5 years. Interestingly, prior to the 1968 Act, the time required for handling *both* CTC (where appropriate) and Product Licence applications was under 8 months in aggregate—i.e. about 12 per cent of total development time. We do, of course, recognise that prior to 1968, the regulatory system was voluntary and evolving. Moreover, it might be argued that since 1968, drug development work has become much more complex, requiring longer development times and correspondingly lengthier vetting of applications by the regulatory agency. Such hypotheses can be tested by considering the evidence on time scales for drugs developed *after 1968.*

5.3 Table III.3 shows time scales for a sample of drugs whose chemical synthesis started before the 1968 Act but which were not marketed until 1970 or later (i.e. so effectively straddling the Act). Compared with the pre-1968 sample (Table III.2), total development times have almost *doubled* (approximately 10 years, a figure also suggested by the questionnaire replies). Similarly, the time required to handle applications for CTCs and Product Licences in aggregate has risen to almost *14 months.* Interestingly, though, this continues to represent a similar proportion of the total development time, namely, some 12 per cent. Also, there has been a substantial rise in the range of variation associated with the handling time for CTCs.

5.4 A comparison of Tables III.2 and III.3 provides further evidence on the effects of the 1968 Act. Consider the time period from chemical synthesis to CTC application. *Before the 1968 Act, this represented 50 per cent of the total development time: for the sample in Table III.3, the corresponding figure was 58 per cent (i.e. of a larger total).* Similarly, the time between first administration to patients and a Product Licence application has increased slightly from under 30 per cent to 32 per cent.

5.5 The data in Tables III.2 and III.3 suggest broad orders of magnitude on the possible effects of the 1968 Act. Assume that the Act explains the *whole* of the increased development time. This suggests an *upper bound* of an extra 4 years 7 months attributable to the legislation (i.e. the difference between 9 years 11 months and 5 years 4 months). However, this is an unrealistic assumption. Other influences such as technical progress are not irrelevant, as indicated in the questionnaire responses. If, then, the Act accounts for, say, 50 per cent of the increased development time (see Questionnaire), *it is responsible for an extra 2 years 4 months in the product development cycle:* a figure which is well within the range of estimates provided by the questionnaire replies.

5.6 Further insights and checks on the reliability of our estimates were obtained by analysing a sample of products developed *after* the 1968 Act—i.e. those where chemical synthesis started in 1968 or afterwards, with UK marketing occurring in the 1970s. Unfortunately, we only received a limited data set and few reliable generalisations were possible. Nevertheless, it seems that the time taken to handle CTC and Product Licence applications in aggregate has increased further to *15 months:* a doubling compared with the pre-1968 situation. The results are shown in Table III.4. The

TABLE III.1
All Drugs, 1958-79

Stage	Time			Number of products
	Average	Range of estimates		
		Minimum	Maximum	
1. Chemical synthesis to UK marketing	8 years	2yrs 3m	13yrs 4m	27
2. Patent to UK marketing	7yrs 1m	2yrs 3m	13 years	25
3. Application to approval of CTC	5.4m	1m	1yr 1m	35
4. Application to approval of Product Licence (letter of intent)	6.9m	1m	2yrs 1m	45

Notes: 1. The sample consisted of products with a starting date for chemical synthesis of 1958, and others which were marketed in the UK in 1979.
2. Product Licence approval is defined by the date of the letter of intent: formal documents are received much later (e.g. up to 1 year later).

TABLE III.2
Time Scales: Pre-1968 Act (n = 12)

Stage	Time	Range of estimates
Medians (unless otherwise specified)		
1. Chemical synthesis to patent	3m	1m—15m
2. Chemical synthesis to pharmacological definition	1m	0m—12m
3. Pharmacological definition to first administration to human volunteers	1yr 11m	6m—38m
4. First volunteers to CTC application (average)	8m	2m—16m
5. Application to approval of CTC (average)	4.2m	3m— 5m
6. CTC approval to first administration to patients	1m	1m
7. First patients to PL application	1yr 7m	10m—33m
8. PL application to approval (average)	3.4m	1m—88m
9. PL approval to first UK marketing (average)	4.25m	0m—15m
10. PL approval to first marketing outside UK	8m	1m—42m
11. Chemical synthesis to UK marketing (average)	5yrs 4m	34m—96m
12. Patent to UK marketing (average)	5yrs 3m	30m—85m

TABLE III.3
Time Scales: 1963-79 (n = 17)

Stage	Time	Range of estimates
Medians (unless otherwise specified)		
1. Chemical synthesis to patent	2m	1m—50m
2. Chemical synthesis to pharmacological definition	1m	0m—12m
3. Pharmacological definition to first administration to human volunteers	4yrs 1m	0—69m
4. First volunteers to CTC application	1yr 7m	8m—37m
5. Application to approval of CTC (average)	5.4m	1m—12m
6. CTC approval to first administration to patients	2m	0m— 6m
7. First patients to PL application	3yrs 2m	4m—65m
8. PL application to approval (average)	8.2m	3m—16m
9. PL approval to first marketing in UK (average)	6.6m	1m—39m
10. PL approval to first marketing outside UK	8m	2m—29m
11. Chemical synthesis to UK marketing (average)	9yrs 11m	79m—160m
12. Patent to UK marketing (average)	8yrs 9m	44m—156m

Notes: 1. As in previous Tables, medians reflect limited data.
2. The sample is based on drugs whose chemical synthesis started before 1968 but were not marketed until 1970 or after.

estimated total development time is substantially less than the figures provided by the questionnaire responses (i.e. namely 8-10 years from patenting to market launch). The difference probably reflects the limited number of observations in Table III.4.

6 Conclusion on time scales

6.1 The development cycle for a NCE is now about 10 years, of which some 60 per cent is allocated to the pre-CTC stage (Table III.3). Clearly, these are substantial investment periods. Their magnitude is even greater if we consider the time from start to CTC approval to administer the product to patients: more than 6 years or about 65 per cent of the total development time! Prior to the 1968 Act, the corresponding time to patient trials was 37 months or 58 per cent of the total development time. Thus, firms now have to bear greater development risks before they can obtain reliable indications of the potential value of a new product (i.e. at the patient testing stage). And such increasing time scales and risks have to be related to a fixed patent life of 20 years (see also questionnaire responses). In these circumstances, the Industry has some justification in claiming that regulation has compelled firms to incur substantial costs at a relatively early stage in the R & D process. For example, the Act has changed the timing of costs, so increasing the costs of failures.

6.2 The 1968 Act has resulted in longer development times, possibly an extra 2.3 years. Within this delay, the licensing authority now takes longer to process applications for CTCs and PLs: a total of 15 months is required, although this figure is *less* than the estimates provided by the questionnaire replies. The difference might reflect the sample of data and a possible confusion about the date of Product Licence approval (i.e. formal documents are received much later than the letter of intent). Nevertheless, the estimate of increased development times attributable to the Act and the trend in the time required by the regulatory agency to handle applications for CTCs and PLs are consistent with the questionnaire findings: handling time has doubled.

6.3 The data suggest that there has been some increase in the delays between regulatory approval and first UK marketing. *Delays at this stage in the product life cycle might have increased from 4.3 months to 6.6 months—a 50 per cent increase during a period when total development times have almost doubled!* Thus, commercial behaviour and motivation do *not* appear to be a major factor in explaining the increased time scales.

TABLE III.4
Time Scales: 1968-79 (n = 14)

Stage	*Time*	*Range of estimates*
Medians (unless otherwise stated)		
1. Chemical synthesis to pharmacological definition	1m	0m—11m
2. Pharmacological definition to first administration to human volunteers	13m	5m—48m
3. First volunteers to CTC application	14.5m	2m—24m
4. Application to approval of CTC (average)	6.2m	1m—13m
5. CTC approval to first administration to patients (average)	8m	0m—19m
6. First patients to PL application	26.5m	14m—68m
7. PL application to approval (average)	8.8m	1m—25m
8. PL approval to first UK marketing (average)	4.5m	0m—18m
9. PL approval to first marketing outside UK	5m	2m—10m
10. Chemical synthesis to UK marketing (average)	6yrs 10m	57m—116m

Note: Insufficient data available on date of patents and, generally, an incomplete data set—e.g. total development time was based on a sub-set of 5 drugs only. Even so the data on application times for CTCs and PLs are each based on 12 observations.

IV THE QUESTIONNAIRE RESULTS

Costs of the 1968 Medicines Act

1 Employment: effects on numbers
(See Appendix A, Questionnaire, Section B, question 1)

1.1 Almost all firms reported that employment had *risen* since the 1968 Act. Predictably, the main categories for increased employment were:

(a) Legal and administrative staff (n = 14).

(b) Testing staff (n = 13).

1.2 Where employment had risen as a result of the 1968 Act, the increases by median and total for the 13 respondents which provided data were:

TABLE B1

	Median increase	*Total increase*	
(a) Legal—administrative	5-6	93	(22%)
(b) Testing	20	224	(53%)
(c) Others	12	103	(25%)
(d) Total rise		420	(100%)
(e) Total employment of firms replying (n = 13)		38,785	
(f) [d] as % of [e]		1.08%	

If this sample is representative of the Industry, it suggests that increased employment due to the Act might be about 1.1% of the total labour force. Alternative estimates were made using sub-sets of the data, as well as medians and 'grossing-up' for the Industry. These alternatives gave estimates of increased employment ranging between 0.8% and 1.9% of the Industry's total personnel. However, few firms believed that the 1968 Act only explained *all* of the increased employment. Most felt that it had made a 'moderate to large' contribution and, weighting the answers by size of firm, suggests that 50% of the increase might be due to the Act. *Thus, the 1968 Act might have raised the Industry's employment by between 300 and 713, say, an extra 500 personnel.* Such figures are no more than broad estimates, giving orders of magnitude. Firms often found difficulty in distinguishing between the employment-raising effects of 'other influences' and the contribution of the 1968 Act.

1.3 Other factors have contributed to higher employment, namely:

(a) Overseas regulatory requirements (n = 6).

(b) Greater technical knowledge and increasing R & D (n = 6).

(c) Increased business and company expansion (n = 5).

1.4 Extra staff have also been required to meet international, rather than UK, regulatory requirements. For each respondent, overseas regulation required a median figure of 9-16 extra staff. A sample of 9 firms estimated a total of 234 extra staff due to *foreign* regulation: this was about 70% of the staff required for UK regulation by the same firms.[38] Thus, the Industry might have to employ between 210 and 497 staff, say 350, in meeting the requirements of overseas regulation. *The result is a grand total of 850 staff (between 510 and 1,210) employed in meeting UK requirements from the 1968 Medicines Act and foreign regulatory demands.*

2 Labour Costs and Production Costs
(Appendix A, Questionnaire, Section B, questions 2-3)

2.1 For each type of labour, the median annual salary in 1980 was:

	£
(i) Legal—administration	6,650
(ii) Testing	6,250
(iii) Other	5,500

For the Industry, the total *salary* costs of the 1968 Act can now be estimated. Assume that 500 extra staff are required and that they are distributed:

TABLE B2

Staff	*% of total**	*Estimated number*	*Median salary (£)*	*Total salary costs (£)*
Legal-administrative	22	110	6,650	731,500
Testing	53	265	6,250	1,656,250
Others	25	125	5,500	687,500
Total	100	500		3,075,250

*Note: * See Section B 1.2 above.*

Thus, the Industry's current annual wage and salary costs due to the 1968 Act are about £3 million (500 staff, 1979-80 prices), although the sum could range between some £1.85m and £4.4m (i.e. based on an extra 300 and 713 staff, respectively[39]). Assuming that labour costs are 110% of wages and salaries, gives an estimated total *labour cost* of £3.381m due to the 1968 Act; and a range of £2.04m to £4.84m. If labour costs are some 59% of total costs, *we might estimate that the 1968 Act is costing the Industry some £5.71m per annum,*[40] ranging between £3.5m and £8.2m (1979-80 prices). This is only an estimate of the annual costs imposed directly upon the Industry and by no means represents the total costs borne by the community.

2.2 A limited number of firms (n = 7) provided data on their UK total costs of production in 1979. This was used to obtain an alternative estimate of the Industry costs of the 1968 Act. For the respondents, costs per man were estimated at £11,339. Applying this figure to the extra 500 staff required by the 1968 Act gives an *estimated cost to the Industry of £5.67m:* an estimate which is similar to the one obtained above.

3 The Preparation and Costs of Submissions

(Appendix A, Questionnaire, Section B, questions 4-5)

3.1 Average figures for the time taken to prepare (i.e. assemble) the documents required for a submission for a CTC and PL, and the associated costs are shown in Table B3.[41]

TABLE B3
Average Time and Cost

Type of submission	*NCE Time*	*Cost*	*Non-NCE Time*	*Cost*
1. CTC	3.8 mths	£13,451	1.4 mths	£4,538
2. PL	4.5 mths	£20,957	1.96 mths	£8,460

3.2 For a NCE, a typical submission for a CTC takes about 4 months and costs some £13,500; the corresponding figures for a PL are 4.5 months and £21,000. However, these figures embrace a range from 3 weeks to 9 months and costs of £2,000 to £100,000! Predictably, the corresponding figures for non-NCEs are much less.[42]

4 Delays: time and costs

(Appendix A, Questionnaire, Section B, question 6)

4.1 *Firms were unanimous that the 1968 Act has delayed marketing, with a median delay of 2 years:* a result which corresponds with replies to other questions (Table 3.1). A number of firms (n = 8) attempted to cost the delays in the form of:

(a) Lost sales revenue per product. The median loss was £2m to £3m.

(b) Lost profits per product. The median loss was £0.5m. One company estimated delays of 3 years, resulting in lost sales revenue of £20m and lost profits of £15m per product.

4.2 These figures provide the basis for two preliminary estimates of *some* of the costs of the 1968 Act. *First,* the 'lost' sales revenue per product provides a broad indication of some of the gross *social costs* of the 1968 Act (i.e. costs imposed on the community, including firms as reflected in the market value of the lost output). *Second,* the lost profits figure gives an estimate of some of the *private costs* of the Act—i.e. the costs imposed on *firms* by the delays (firms are only *part* of the community).

4.3 For the 8 respondents and each of their typical products, lost sales revenue *totalled* £48.2m or £6.025m per firm per product. Similarly, lost profits totalled £21.65m or £2.7m per firm per product. Spread over a two year period (delays of two years), gives lost sales revenue of £3.01m and lost profits of £1.35m *per product per annum.* Studies of the 1969-79 period suggest that the UK Industry produced 10-12 NCEs per annum.[43] On this basis, *delays* due to the 1968 Act might be costing:

(a) Private industry some £13.5m to £16.2m per annum, say, £15m in lost profits.

(b) The community some £30.1m to £36.12m per annum, say, £33m as reflected in lost sales revenue.

5 Estimating the Costs of the 1968 Act

5.1 *Methodology.*[44] Three sets of costs can be identified:

(1) Costs imposed on the Industry as a direct result of the Act-e.g. the costs of testing, legal staff and fees.

(2) Indirect costs due to delays in marketing new products.

(c) Indirect costs associated with products which never reach the market.

Estimates of the *social costs* of the 1968 Act (i.e. costs borne by the community, namely Industry and consumers) are inevitably complex and the results of this study are no more than tentative orders of magnitude. For example, without the Act, would the Industry bear any of the direct costs of regulation? Similarly, are the products which never reach the market a *desirable* (socially beneficial) result of the Act, and hence should *not* be regarded as one of its costs? There are also dangers of double-counting, especially between current products, delayed drugs and those which fail to appear. In the circumstances, we proceeded by calculating upper and lower bound estimates and offering a best guess.

5.2 *Estimating the losses due to drugs which are never marketed.* The Act has dynamic effects in the form of the marketing of fewer new drugs. Estimates of dynamic effects are inevitably tentative. Moreover, supporters of the 1968 Act might refuse to accept such estimates of lost profits and sales as part of the calculation of social costs. We shall proceed by providing an estimate as a contribution to the debate.

Assuming that R & D recovery rates are 10% of sales, then lost sales revenue of £33m. (B4 above) represents lost research expenditure of £3.3m. People discover drugs and the lost research effort associated with the lost sales revenue might exceed 300 people. Research productivity is highly uncertain, but one firm in the sample suggested this lost research effort might represent the loss of a major NCE drug every 2-3 years. The resulting social costs will depend on society's valuation of the lost drugs. Three estimates provide some possible orders of magnitude (see B4):

(i) The median estimate of lost sales revenue per product, namely £2m to £3m, say £2.5m.

(ii) The average estimate of lost sales revenue per product, namely £6.025m.

(iii) The maximum loss of sales revenue reported in the questionnaire results, namely £20m.

Assume that the lost sales revenue accrues over a 2 year period.[45] On this basis, the lower bound estimate of the resulting lost profits is £0.6m per year and the upper bound is £4.5m per annum, with a best guess of £1.4m.[46]

5.3 *Cost estimates.* For the UK, the 1968 Act involves:

(a) Costs of some £6m (± 2.5m) per annum for the Industry in *directly* responding to regulatory demands (e.g. testing, legal staff); *PLUS*

(b) Costs of £2.7m per year on sub-contract R & D work required by the 1968 Act; *PLUS*

(c) Costs of £3m per annum on quality control and £1m per year on extra selling expenses; *PLUS*

(d) Costs imposed on the Industry through licence fees. Under the Medicines Act 1968, the holders of licences and certificates are required to pay fees to defray part of the costs of operating the licensing system. For 1979-80, total DHSS income from fees was £3.06m.

(e) Losses associated with delays of 2 years. These comprise lost profits of £15m per annum which are also included in the social costs of £33m per year of lost sales revenue attributable to delays caused by the Act.

(f) Losses associated with products which never reach the market (i.e. dynamic effects), estimated at some £3m per annum in lost sales revenue, including £1.4m per year in lost profits.

5.4 *Costs imposed on the Industry.* The costs imposed on the Industry, or private costs, consist of direct costs (items a + b + c + d above) plus lost profits from both delays and drugs which never reach the market (items e + f above). On this basis, the 1968 Act might be costing the UK Industry about £32m per annum. Ideally, this figure should be revised downwards since, in the absence of the Act, the Industry will continue to regulate itself: hence the savings in direct costs might be 50% (£8m rather than some £16m),[47] giving *a revised best guess of some £25m per annum.* On more favourable assumptions, the estimate could approach £40m per year. The range of estimates of Industry costs is summarised in Table B4. *An estimate of some £25m is equivalent to 1.2% of the Industry's sales, or 11% of its R & D expenditure (1979).*

TABLE B4
Costs imposed on the Industry *1979 (£m)*

Item	*Best guess*	*Lower bound estimate*	*Upper bound estimate*
Direct costs			
Staff, etc.	6.0	3.5	8.2
Sub-contract R & D	2.7	2.7	2.7
Quality control and selling	4.0	4.0	4.0
Licence fees	3.06	3.06	3.06
Sub-total:	15.76	13.26	17.96
Lost profits due to:			
i) Delays	15.0	13.5	16.2
ii) Drugs not marketed	1.4	0.6	4.55
Total £m	32.16	27.36	38.71

6 The Social Costs of the 1968 Act

Estimates of social costs or costs imposed on the community are even more difficult and tentative. Estimates have to be made of the totality of resource inputs in both the public and private sectors, with care required to avoid double-counting. Thus, estimates are required of the effects on the community of the delays and drugs which never reach the market. A starting point is the size of the public sector regulatory industry.

6.1 *The size of the UK public sector regulatory industry.* Employment in the *public sector* regulatory activities associated with the 1968 Act consists of:

	Numbers
(a) DHSS Medicines Division Staff	282 (+20 vacancies)
(b) Medicines Commission membership	19
(c) CSM membership	22
(d) CRM membership	23
(e) Doctors employed part-time on investigating reports of adverse reactions	80
(f) Other staff in outside agencies, laboratories, etc., not included elsewhere	not available
Total numbers	446

Thus, the 1968 Act involves some 450 people, although not all are employed full-time on regulation associated with medicines for humans. Some are employed on veterinary products whilst the members of various Committees are only part-time. Estimates were also obtained of the involvement of members on the CSM and CRM:[48]

	CSM	*CRM*
Number of meetings	12	6
Average duration of meeting	4½ hrs	2½ hrs
Membership	22	23
Average attendance	17	19
Total man hours per year in Committee	918	285
Number of sheets of paper (A4) per member per meeting	500	less than 500
Travelling, subsistence and other expenses	£13,100	£5,900

These figures are by no means trivial. During 1978, the CSM and CRM together involved a total of 1,200 man hours in actual *Committee* meetings, with each member receiving 6,000 sheets of paper

for the CSM and somewhat less for the CRM. And these figures are not an accurate estimate of the true *time* costs of membership. Each meeting requires further time inputs for the preparation and reading of papers (500 sheets), post-meeting discussions, and travelling. Our guesstimates of these magnitudes are:

(a) Reading and preparation per member per meeting = 1 day

(b) Travelling time per member per meeting = 4½ hrs

(Members are distributed between London, Wales, Midlands, North and Scotland; and it is also assumed that some preparation is undertaken whilst travelling.)

Applying these figures to the CSM and CRM produces an aggregate of almost 650 man days of time input for Committee members during 1978.[49] And time is valuable. Committee members are leading professionals, so that they are highly-paid. Assuming an average rate of £100 per day (1978 prices), gives a true labour cost for CSM and CRM involvement of £65,000 (650 x 100). Travelling and subsistence expenses for the two Committees were £19,000 in 1978. There are also supporting (overhead) costs for Committee members—e.g. use of offices, homes, heating, light, etc., for the reading of papers and preparation for meetings.[50] *Combining these estimates suggests that the true costs for society of membership of the CSM and CRM was some £150,000 in 1978* (i.e. much larger than the notional travelling and subsistence expenses). It must be stressed that these estimates are for Committee members only: the staff of the DHSS Medicines Division are excluded, since they are the subject of a separate costing exercise (see below). Ideally, a similar exercise is required for the true costs of the Medicines Commission membership and the doctors employed part-time on investigating reports of adverse reactions.

6.2 *The costs of the DHSS Medicines Division.* The licence fees levied on the UK Pharmaceutical Industry are designed to cover the licensing costs of the 1968 Act. Fees represent about 65 per cent of the staff and on-costs of the Medicines Division and the corresponding Division of the Ministry of Agriculture, together with a proportion of the costs of the various Committees, inspectorate work, sampling and automatic data processing. The costs of the DHSS Medicines Division and related expenditures for 1976-81 were:

	1976-77	*1977-78*	*1979-80*	*1980-81*
(i) Licensing costs chargeable to fees (£m current prices)	1.81	2.06	3.03	3.60
(ii) Total costs (£m current prices)	2.79	3.20	4.67	5.54

Source: Medicines Commission, *Annual Reports*. HMSO, London.

Such estimates are important in showing that the licence fees are only *part* of the *public sector's* regulatory costs. In 1978, public sector regulation was costing society over £3.3m (allowing for the true costs of the CSM and CRM); and for 1979-80, the sum exceeded £4.8m.[51] These are broad orders of magnitude. We recognise that such cost estimates are subject to many limitations, often pointing in opposite directions:

(a) There is some double-counting in that licence fees cover part of the *travelling and subsistence* expenses of the Committees involved in regulation.

(b) A veterinary element is contained in the totals.

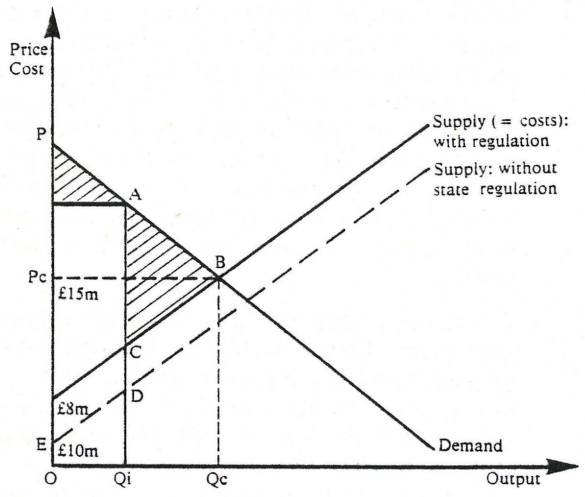
(c) We have excluded a true cost estimate of the Medicines Commission, part-time doctors and any other inputs required by the 1968 Act (e.g. laboratories).

(d) We have assumed that DHSS outlays are indicators of the true costs imposed on the community. For example, we have not attempted to estimate the true social costs (market value) of any Government-owned property used by public sector regulatory staff.

With these limitations we believe that, on balance, the figures given above are likely to be conservative estimates. *Thus, in 1979-80, the DHSS Medicines Division, its associated Committees and doctors involved in regulating drugs for humans were costing society some £5m per year.* Once again, it has to be emphasised that these are only the public sector costs of regulation (i.e. DHSS, *et al.*). The *total* social costs are obtained by adding to this sum, the costs of lost output, as well as the costs imposed on the Pharmaceutical Industry.

6.3 *The social costs of lost output.* A starting point is the annual value of lost sales revenue associated with both delays and drugs which are never marketed, namely, £36m per year,[52] *plus* the net costs imposed on the Industry as a direct result of the Act, estimated at £8m per annum (50% of £15.76 in Table B4). The resulting total of £44m per year[53] might be regarded as a crude reflection of society's valuation of the lost output due to the Act. As such, the estimate measures the area under market demand curves, so including both lost profits and production costs, as well as the costs imposed by regulatory demands (e.g. staff and licence fees). Nevertheless, it is a crude estimate of costs imposed on the community and its potential limitations are outlined in Figure 1. It can be seen that the estimated lost sales revenue omits some consumer valuation, namely, the loss of consumer surplus shown by the area $P_1$1PA in Figure 1. Also, insofar as markets are monopolistic, there are further losses associated with producing an output below the competitive level (area ABC in Figure 1). Moreover, the analysis is only a *partial equilibrium* which neglects the widespread impact on prices, sales and profits of *existing products* following the introduction of more new drugs onto the market. Accurate estimation is clearly a complex task. For simplicity, it will be assumed that:

FIGURE 1



Notes on Figure 1 This diagram is illustrative and is based on the *case of drugs which are delayed.* Assume that the price-output combination of the new drugs would be P_1Q_1 = £33m (i.e. profits of £15m and costs of £18m including direct regulation costs of £8m). At output Q_1 there would be additional consumer valuation shown by P_1PA (not reflected in P_1Q_1). The competitive output is P_cQ_c which would give extra net gains shown by ABC. Estimates of lost revenue are equivalent to estimating OP_1AQ_1. Our assumptions restrict the estimated net social costs to the area EP_1AD (represented as producer surplus).

(a) A true estimate of the *net* social loss due to the 1968 Act can be represented by the difference between the demand and supply (cost) curves, as shown in Figure 1.

(b) Output will remain less than the competitive level (Q_1 in Figure 1): hence, we shall ignore any social losses due to output being 'too low'.

(c) The consumer valuation not included (area P_1PA at Q_1) equals any offsetting adverse effects on *existing* products.

(d) In the absence of the 1968 Act, some regulatory staff will continue to be employed as firms use modified, more efficient and cheaper, testing procedures.

These simplifying assumptions form the basis for estimating the true social costs of the 1968 Act.

6.4 *The total social costs of regulation.* The true costs of the 1968 Act consist of the *total costs borne by the community.* These comprise the direct costs of regulation (e.g. employment in the private and public sectors associated with legal, administrative and testing work, etc.), and its direct effects on patients through delays in the introduction of new drugs and the effects on patients of products which never reach the market. Our study has provided some broad estimates of the social costs of the 1968 Act:

	£m (1979 prices)
(i) *Direct Social Costs*	
(a) Increased employment in the Pharmaceutical Industry (500 staff)	6.0
(b) Sub-contract R & D (200+ staff)	2.7
(c) Quality control and selling	4.0
(d) DHSS, *et al.* (including licence fees: approximately 450 staff involved, full or part-time)	4.8+
Sub-total:	17.5+
(ii) *Indirect Social Costs*	
(a) Value of delays and non-marketing	16.4
Total:	33.9+

Some of the direct costs might be revised downwards to allow for the Industry regulating itself in the absence of the 1968 Act. One possibility is a 50% downward adjustment in direct social costs. Alternatively, it might be argued that without the Act, all the DHSS inputs would be abolished and the 50% adjustment should only apply to the remaining direct costs. *Thus, the 1968 Act could be costing the community some £25m-28m per annum (1979 prices).*[54] This is a conservative estimate. Much depends on the assumptions used to estimate the indirect social costs. For example, if the true costs of production are relatively small compared with the final selling price,[55] then the estimated social costs will be correspondingly greater, and, in the limit will approach the value of lost sales revenue and *net* regulatory costs, namely, £45m-47m per annum. Indeed, on this basis, taking the upper bound of gross direct regulatory costs and the highest estimates of lost sales revenue, gives a maximum possible social loss of £66m per year due to the Act.[56] To summarise, the true social costs of the 1968 legislation might be in the region of £25m-28m per annum, with an upper limit of £66m per year. A best guess might be the average of the £25m-28m and £45m-47m estimates, some £36m per annum (1979 prices). What are the results of such costs and is the present level of regulation worthwhile?

V WHAT ARE THE BENEFITS OF REGULATION?

1 Performance Indicators

A cost-benefit analysis of the 1968 Act cannot ignore the potential benefits of the legislation. Questions arise about patient safety and the case which might be presented in defence of regulation. How can society assess the 'performance' of the

DHSS regulatory agencies?[57] Various output and performance indicators have been suggested:

(a) *The length and content of Annual Reports.* For example, the length has increased from 8 pages in 1971 to over 100 pages in 1978!

(b) *Numbers of MALs, Orders-Statutory Instruments and Regulations.* Between 1970 and 1976, there was an average of some 10 Orders-Regulations per year, covering items such as fees, advertising and child safety. Also, by 1978, there were 99 Medical Advisory Leaflets, providing information on the operation of the Act.

(c) *The growth of DHSS Medicines Division Staff.* Numbers rose from 195 staff in 1973 to an establishment of 302 in 1978 (282 staff and 20 vacancies): an increase of 55 per cent, which is substantial on any criterion!

(d) *Inspection and enforcement activities.* For example, in 1977 inspection involved over 1,000 inspector days, with visits to manufacturers, wholesalers and hospitals, both in the UK and overseas.

(e) *Post-marketing surveillance and the dissemination of information.* The number of reports of suspected adverse reactions rose from 4,818 in 1974 to 11,873 in 1978. In this way, the CSM might be providing a valuable function acting as a central agency increasing the amount of useful (worthwhile) information in the market.

(f) *The review of existing medicines.* Following the formation of the CRM (1975) and its initial enquiries, some 10,000 licences were surrendered voluntarily.

(g) *Changes in testing procedures.* For example, in 1976, new testing requirements were introduced for CTCs.

(h) *Licensing activities.* Here, two output indicators are available, namely, the number of applications received and processed and the average time taken to process applications. Data on the licensing activities of the CSM 1975-78 are shown below:

	1975		*1976*		*1977*		*1978*	
	PL	*CTC*	*PL*	*CTC*	*PL*	*CTC*	*PL*	*CTC*
1. Number of applications to CSM	328	104	506	127	601	120	589	108
2. Number of applications approved	235	78	237	91	158	45	113	30
3. Number of applications refused	14	—	9	3	16	2	13	2
4. Number of applications withdrawn	16	13	45	10	39	11	8	1
5. Applications outstanding	162	38	315	56	332	50	408	67
6. Staff of DHSS Medicines Division	216		267		288		282	

Note: PL = Product Licences; CTC = Clinical Trial Certificates.
Sources: Medicines Commission, *Annual Reports*, HMSO, London, 1976-78.

Between 1976 and 1978, the CSM received over 600 applications per annum. Few appliations were refused. However, between 1976 and 1978, there was a substantial decline in the number of applications approved. Furthermore, staff in the DHSS Medicines Division increased by 31 per cent between 1975 and 1978, but applications outstanding more than doubled![58] Within this framework, the DHSS claims that a substantial number of Product Licence applications are determined within 120 days of submission, or in exceptional circumstances within 210 days (figures which are lower than the estimates obtained in the Questionnaire evidence and the data on time scales).

The various 'performance' indicators *appear* impressive. They are, though, misleading measures of output. All are inputs or measures of intermediate, rather than *final,* output: *they do not tell us the effects of the 1968 Act on the actual consumers of medicinal products and how highly consumers value any such effects.* Supporters of regulation would obviously claim that it has resulted in a 'substantial' (worthwhile?) improvement in safety for the users of medicinal products. Such claims require some consideration of the benefits and risks from new drugs.

2 Risk-benefit ratios

The use of medicines requires choices about the likely benefit from the product in relation to its costs and any associated risks in the form of expected or unexpected side-effects. Here it has to be recognised that *even with the 1968 Medicines Act,* no medicines can be regarded as totally safe. There is always a *risk.*[59] Even after exhaustive and comprehensive testing there may well be hazardous properties of the medicine which have yet to be observed. Perhaps the current state of scientific knowledge is incapable of detecting the potential hazard. In some products, problems may not be observed until many years later, probably in different generations. Nor do statistical associations necessarily imply *causation* (e.g. there might be undetected bias or other influences which have been neglected in the tests). Significantly, the UK Medicines Commission accepts that 'no medicines can be regarded as completely safe. There is always a risk ... of adverse side effects. It is ... impossible for any practicable programme of testing, or of evaluation of the testing by supervisory bodies, to offer an absolute safeguard'.[60]

A reading of the various *Annual Reports* of the Medicines Commission confirms the risks associated with medicinal products. Some examples are:

(a) Prazosin. Following the use of Prazosin (a new anti-hypertensive drug), some patients collapsed suddenly with the loss of consciousness and some had to be admitted to hospital. However, many patients received larger doses without ill-effects (Annual Report, 1975, p.20).

(b) Practolol involved some adverse reactions to the eyes and skin (Annual Report, 1975, p.20).

(c) Possible associations between hormonal pregnancy tests and congenital abnormalities (Annual Report, 1977, p.22).[61]

Given that no medicines are completely safe, has the 1968 Act contributed to improved safety? And would society be willing to pay, say, £25m-36m per annum for any such improvements? The questionnaire results showed that the Pharmaceutical Industry believed that the 1968 Act had not resulted in a substantial improvement in patient safety. Firms were, however, unanimous that the Act has had *harmful* effects through delays in the introduction of new drugs. For example, one US study estimated that the 11 years of delay in the introduction of beta-blockers into the States killed a quarter of a million Americans.[62] In other words, regulatory authorities have tremendous potential for harm in preventing improved products from reaching patients who need them. In the circumstances, can the activities of the regulatory authorities be defended?

3 The DHSS regulatory activities: A case for the defence?

Various arguments have been used to defend DHSS regulatory policy. These include

(a) *Regulation has reduced the 'excessive' number of drugs on the UK market.* But this is a disturbing argument since bureaucrats and committees are making judgements on behalf of society without allowing the community (e.g. voters; patients) to express its preferences for different amounts of risk.

(b) *The reporting of adverse reactions has improved the operation of the market for medicinal products.* But, if information deficienies are a major cause of markets failing to work properly, it is far from clear that the 1968 Act is the only, nor necessarily the most appropriate, solution.[63]

(c) *It is claimed that the costs of the 1968 Act are relatively small and, in its absence, the Pharmaceutical Industry would continue to be subject to foreign regulatory requirements.* Clearly, the magnitude of 'relatively small' is an empirical issue. This study suggests a figure of £25m-36m per annum (1979 prices).[64] Moreover, relatively greater foreign regulatory requirements will improve the relative attractiveness (competitiveness) of the UK as a centre for pharmaceutical R & D.

(d) *It is alleged that the DHSS has not had an adverse effect on 'real' innovation.* Policy-makers claim that in recent years, most of the Industry's R & D effort has contributed to *small* changes with little innovatory effect, so resulting in 'excessive' product differentiation. The policy view is that greater, or less, or the existing amounts of regulation have *no* effect on *real* innovation. Such claims resemble a view or model in which innovation simply happens (i.e. autonomous), almost regardless of the efforts of Industry and state controls. Alternative models of innovation[65] stress the contribution of market structure (competition), private ownership, size of firms, R & D expenditure, and previous experience. Evidence is also required. This shows that the introduction of NCEs into the UK declined from an annual rate of about 30-40 in 1960 to 15-20 in the mid-1970s; and the decline occurred at a time of greater Government regulation on the safety of new drugs.[66] But correlation does not necessarily imply causation. Drug innovation is likely to be influenced by a variety of factors, with state regulation as only one variable in a complex model. In this context, the questionnaire evidence provided useful insights. The Industry claimed that the 1968 Act has had a major adverse effect on its R & D activity, resulting in longer development, less innovations, less basic research, and more clinical R & D being undertaken abroad.

(e) *The DHSS is often criticised for contributing to delays; but it makes the point that delays are often caused by companies, through postponed marketing after receiving a Product Licence!* These are testable hypotheses. The typical delay caused by companies between Product Licence approval and UK marketing might be 4-7 months. In other words, companies also cause delays, but these are substantially less than the delays attributable to the licensing authorities. And in the case of company-induced delays, the costs are more likely to be borne by those responsible for such marketing decisions.

VI SUMMARY AND CONCLUSIONS

1 The case for the UK Pharmaceutical Industry

(a) The UK Pharmaceutical Industry is an R & D-intensive sector, as well as a major employer and contributor to the balance of payments. In 1975, it accounted for some 6 per cent of total UK manufacturing industry R & D. It is obviously a risky activity: typically, the ratio of UK drugs marketed to drugs tested is 1:12,000 (i.e. 11,999 do not make it). Such R & D-intensive industries are believed to be the basis for maintaining or improving Britain's *future* international competitiveness, particularly as third world nations become increasingly competitive in traditional manufacturing industries.[67]

(b) An official study concluded that the Industry '... is one of the strongest sectors of the UK economy ...' and that a key factor in its success is a 'thriving R & D base'. However, the

study recommended that to retain the UK's comparative advantage as a centre for R & D '... drug approval procedures should be more speeded up ...' aiming for a three month lag between an application and a decision.[68]

2 The costs of the 1968 Medicines Act

Regulation is not costless:

(a) The Act absorbs *over* 1,000 staff (full-time equivalents) in Industry and Government.

(b) The Act has led to delays in the marketing of new drugs, possibly an extra *two years* or more. Such an increase has to be related to a trend towards lengthier development periods, currently requiring some 10 years for a new product.

(c) There has been an adverse effect on innovation (i.e. fewer new drugs are marketed).[69] This, together with delays, has had harmful effects on patients.

(d) UK-owned firms reported a *decline* in the proportion of their R & D undertaken in the UK.

(e) The licensing authority takes almost 10 months to handle CTC applications and about one year for Product Licences. These time periods have *increased* due to:

(i) A shortage of qualified licensing authority staff;

(ii) Increased regulatory requirements.

(f) Documents submitted to the licensing authority are substantial volumes. The combined applications for a CTC and a Product Licence exceeds 4,000 pages and requires over 8 months of preparation at a cost of £35,000 (1979 prices).

(g) The total cost of these effects could be £25m-28m per annum (1979 prices), and this is a conservative estimate. In other words, expressed in *1981 prices* the Act could be costing the community more than £30m per year (with an upper limit in the region of £85m per annum).

3 Is the Act worthwhile?

(a) Presumably, society would regard regulation as worthwhile so long as its expected benefits were at least equal to its costs. On this basis, the benefits have to exceed £30m per annum (1981 prices).

(b) Various benefits have been claimed, although many are of dubious validity:

(i) The legislation has eliminated 'undesirable cowboys and bandits'. But in doing so, the Act has encouraged *exits* from the market so *reducing* competition!

(ii) Drugs are now safer, to the benefit of patients. But such claims lack any empirical basis. Our results contribute by introducing some quantification into the policy debate. Is society willing to pay over £30m per year for any improved safety due to the 1968 Act? Also, it cannot be stressed too often that all drugs involve some risk. Regulation probably adds to the *mistaken* belief that drugs are perfectly safe and involve no risks. But then perhaps the legislation 'protects' vote-sensitive politicians and administrators rather than patients!

(iii) For an Act which is supposed to benefit patients, one example of its operation is revealing. It has been asserted that if aspirin and penicillin were new drugs, they would be unlikely to pass current regulatory requirements!

(c) A study of the effects of the 1968 Act on the UK Home Medicines Industry concluded that '... the net social benefits of the legislation may well turn out not only to be negative but to be significantly so'.[70] Our own study suggests a similar conclusion applies to the wider market for pharmaceutical products for human use. In which case, what are the alternative policy solutions?

4 What are the alternatives to the 1968 Act?

There are two broad sets of options for public policy, each of which needs to be subject to a cost-benefit appraisal:

(a) *Introduce a degree of De-Regulation within the framework of the 1968 Act.* The possibilities include:

(i) Greater flexibility, fewer delays and less bureaucracy. Here, the US system of different priorities might expedite CTC and PL applications.

(ii) Reform the CTC system.[71] In particular, allow earlier clinical trials in humans. This would allow the earlier termination of unsuccessful products, so increasing resources available for new developments, as well as benefiting patients from the earlier introduction of valuable new medicines.[72]

Thus, modest de-regulation is likely to be socially beneficial. It will reduce the costs of the existing system and medical experts believe that there would be no increased risks to patients. At the same time, if foreign nations continue to *increase* their regulatory requirements, there will be an improvement in the *relative competitiveness* of the UK as a centre for Pharmaceutical R & D.

(b) *Dismantle the existing regulatory framework, replacing it with voluntary self-regulation (cf. CSD) and possibly some form of insurance arrangement.* For example, the Government could establish a fund to compensate people who suffer from unforeseen side effects as a result of consuming medicinal products. Or, manufacturers could be made liable for product defects. Alternatively, society

might decide that drug victims are not unique and that the 'appropriate' solution is to provide adequate income deficiency payments to those in 'need'. Or, the community might prefer to concentrate on increasing the amount of information available to patients.

Clearly, the alternatives are not necessarily mutually exclusive. The point to be made is that the present regulatory system has its deficiencies, with doubts about its social desirability. Nor is the present system the only solution: there exists *a range of alternatives*. In the circumstances of mounting criticisms and genuine doubts about the value of the 1968 Medicines Act, we would argue that now is the time for a serious re-appraisal of the UK's regulatory arrangements.

FOOTNOTES

1 *Acknowledgements.* We are most grateful for advice, comments and assistance from Professor G. Teeling-Smith, OHE, Mr. D. Massam, Mr. R.D. Smart and Mr. J. Spink. We are especially indebted to the many individuals in the Industry who devoted a considerable amount of their scarce time to responding to the questionnaire and our early results, as well as to officials in the DHSS for providing an alternative view. As usual the authors must retain property rights for any errors and omissions that remain in this study.

2 Review Board for Government Contracts, *Report on the Second General Review of the Profit Formula for Non-Competitive Government Contracts,* HMSO, London, 1977, also K. Hartley and P. Watt, Profits, Regulation and the UK Aerospace Industry, *Journal of Industrial Economics,* vol. XXIX, June 1981, pp.413-428 and A. Maynard, Competition Policy, Industrial Policy and Transport Policy, in D. Dosser, D. Gowland and K. Hartley (eds.) *The Collaboration of Nations,* Martin Robertson, 1982.

3 M.W. Jones-Lee, *The Value of Life: An Economic Analysis,* Martin Robertson, London, 1976 and G.H. Mooney, *The Valuation of Human Life,* Macmillan, London, 1977.

4 This method of economic evaluation, cost-effectiveness analysis, has been used to evaluate other aspects of the drug industry—e.g. the cost-effectiveness of alternative means (i.e. different drugs or drugs vis à vis surgery) of achieving given therapeutic ends: see A.J. Culyer and A.K. Maynard, The costs of dangerous drug lesiglation in England and Wales, *Medical Care,* 8, 501, 1970, and A.J. Culyer and A.K. Maynard, The cost-effectiveness of duodenal ulcer treatment, *Social Science and Medicine,* 15C, 1, 1981.

5 ABPI, *The pharmaceutical industry and the nation's health,* London, 1980.

6 Department of Health and Social Security, *The Control of Medicines in the UK,* MAL 99, July 1977, London.

7 M. Cuthbert, J.P. Griffin and W.H.W. Inman, The United Kingdom, in W.W. Wardell (ed.), *Controlling the Use of Therapeutic Drugs: An International Comparison,* AEI, Washington, DC, 1978.

8 MAL 99, *op cit,* p.28.

9 J.P. Griffin, Introduction to UK Drug Regulation in J. Powers and G.P. Velo (eds.), *Drug Assessment: Criteria and Methods,* Elsevier-North Holland Biomedical Press, 1979, p.27.

10 Cmnd 3395, *Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines,* HMSO, London, 1967.

11 For a history of this development see P. Temin, The Origin of Compulsory Drug Prescriptions, *Journal of Law and Economics,* 22, 1, 91-106, 1979.

12 A.L. Cochrane, *Effectiveness and Efficiency: random reflections on health services,* Nuffield Provincial Hospitals Trust, 1972, and A. Maynard, The inefficiency and inequalities in health care systems in Western Europe, *Social Policy and Administration,* 15, 2, 145-63, 1981.

13 Keith Hartley and Clem Tisdell, *Micro-Economic Policy,* J. Wiley, London, 1981, and A. Maynard, The economics of public choice, in D. Gowland (ed.), *Modern Economic Analysis,* Butterworths, London, 1979.

14 G.J. Stigler, The Theory of Economic Regulation, *Bell Journal of Economics and Management Science,* Spring, 1971, and A. Maynard, How not to regulate the medical profession, in R.A. Leaper (ed.), *Health, Wealth and Housing,* Basil Blackwell, 1980.

15 DHSS, Medicines Commission, *Annual Report,* 1978, HMSO, London, HC 163, Appendix III, Product Liability.

16 An initial draft of the questionnaire was formulated after discussion with the ABPI, a limited number of companies and DHSS. This draft was further discussed with ABPI and a small working party of industry representatives offered additional comments and suggestions. We are most grateful to all those who helped to formulate the questionnaire, as well as to the respondents: the usual disclaimers apply.

17 This part of the questionnaire was similar to one used by Wardell: see W. Wardell, The drug lag revisited: comparison by therapeutic area of patterns of drugs marketed in the US and Great Britain, 1972-78, *Clinical Pharmacology and Therapeutics,* 24, 5, 499-524, November 1978.

18 K. Hartley and C. Tisdell, *Micro-Economic Policy,* J. Wiley, London, 1981.

19 The questionnaire was accompanied by a supporting letter from the President of the ABPI, Mr. R.D. Smart. Initially, responses were requested by mid-March, 1980. This deadline proved too optimistic.and was extended.

20 The researchers suggested an interview-questionnaire study—i.e. interviewing each firm in the sample using the questionnaire as the basis for a structured interview. However, there were major constraints of time and available resources, hence the use of the postal questionnaire. It must also be stressed that prior to formulating the first draft of the questionnaire, we visited a number of major firms, so that we had some 'first hand' knowledge and experience of the Industry and its beliefs.

21 Five of the ten were UK-owned firms, accounting for 70% of employment in the sample, so reducing any bias which might have arisen if the responses had been dominated by foreign-owned firms (e.g. foreign enterprises might undertake clinical studies in the parent country).

22 The figures do not correspond to the data in Table 4.1 due to the use of medians.

23 One firm explained that the small reduction in its percentage of R & D to sales reflected accounting changes between 1968 and 1979. In fact, its R & D expenditure in this period increased by $7\frac{1}{2}$ times.

24 G. & P. Polyani, *Competition, risk and profit in the pharmaceutical industry,* ABPI, London, 1975.

25 Assuming 1.33% of sales for quality control and Industry sales of £1,995m in 1979.

26 The Industry estimates are based on Table 6.2 capital costs of £1.2m and annual costs of £118,000.

27 See Section 6.2 and Table 6.2: £6.2m x $\frac{1}{2}$ = £3.1m per year. Capital costs have been omitted since such expenditures have already been incurred and are 'byegones'. However, they are relevant in *future* replacement decisions. Assuming a 10 year 'life' for fixed assets and capital costs of £63m gives an average expenditure of some £6.3m per year. Assume that with a voluntary system only half of this would be 'saved': *hence savings on capital costs might average some £3m per annum without the Act.*

28 This estimate was obtained by weighting the responses by employment and then 'grossing up' for the Industry—i.e. assuming the sample represented 75% of the Industry.

29 Ranked first 7 and 5 times, respectively.

30 One firm commented on the substantial *waiting time* between the stages of the review process and involving the secretariat, sub-committees, main Committee and licensing authority. From correspondence, the firm has estimated that the time when applications are under professional scrutiny are:

	Pharmacy-Chemistry	*Medical-Toxicology*
(a) Professional secretariat	5-7 days	7-10 days
(b) Sub-Committee	1 day	1 day
(c) Main Committee (CSM)	1 day	

Allowing an additional 14 days for postal delivery time to Committee members results in a total *active* time of about *40 days.*

31 For example, some nations might rely upon prior marketing in a developed and highly regulated nation (i.e. free rider effect).

32 A sixth rank has been reported in view of the number of firms mentioning this response and its similarity with other replies, so that it adds to the total 'picture'.

33 One firm expected costs to fall, 'but prices are affected by other factors, but would also fall'. However, this firm did not give a price fall a priority ranking.

34 Some economic models suggest that regulation protects an industry from new entrants, including foreign competition.

35 An alternative view is that regulation protects an industry and benefits producers.

36 See also Appendix B, which outlines the results of a statistical analysis of firms.

37 K. Hartley and W. Corcoran, The Time-Cost Trade-Off for Airliners, *Journal of Industrial Economics,* March 1978.

38 The 9 firms required 234 extra staff for overseas regulation and 337 extra staff to meet UK regulatory requirements: hence overseas staff is 0.7 x UK.

39 12 firms provided employment and salary data and specified the broad percentage contribution of the 1968 Act. For these firms, we estimated that the salary costs due to the Act were £1.24m: grossing-up for the Industry gave an estimated annual salary cost of £2.5m attributable to the Act.

40 The 59% labour to total costs is based on figures for the UK Chemicals and Allied Trades.

41 Averages are used because the medians failed to distinguish any cost differences between a CTC and PL for NCEs: in each case the median cost was £10,000, with median times of 3-4 months and 3-6 months, respectively.

42 These figures can be applied to the annual number of submissions to provide an alternative estimate of the *administrative* costs imposed on the Industry by the 1968 Act (i.e. excluding testing costs, etc.).

43 Data provided by OHE. Lost sales = 3.01 x 10 to 12 = 30.1 to 36.12 in lost sales revenue.

44 Throughout, we have tended to be cautious and conservative in our estimating: hence the figures are likely to be reliable, but lower bound, estimates.

45 See also the assumptions made below to calculate the static social costs of the Act: Figure 1.

46 Halve each of the estimates of lost sales revenue to obtain annual figures. Assume that profits are 45% of sales revenue (i.e. 15 ÷ 33): hence the minimum estimate of £0.6m. The upper bound assumes that production costs are zero. The best guess is based on the average estimate of lost sales revenue = £6.025m.

47 The best guess of direct regulatory costs is £15.76m: it is assumed that in the absence of the Act, self regulation would be cheaper but not costless—hence the 50% figure. Alternatively, it might be argued that without the Act, licence fees would be abolished and the remaining direct costs might be halved, so that the savings in direct costs might be £9.4m per annum. The result would be a cost estimate approaching £26m per annum.

48 Estimates for 1978 were kindly provided by the CSM: the usual disclaimers apply. All the estimates of public sector employment are for 1978.

49 Assuming an 8 hour day. Also, the allowance for reading and preparation per member for each meeting (500 sheets of paper) is probably an under-estimate, and might require at least another one-half day: this would raise the total time input to about 1000 man days per annum.

50 Assume an overhead recovery rate equal to labour costs (100%).

51 Allowing for an inflation element on the true (1978) costs of the CSM and CRM.

52 Estimated lost revenue of £33m due to delays and an average of £3m (50% of £6.025m) due to drugs not marketed: see section on *Estimating the losses due to drugs which are not marketed.*

53 In this estimate, the element of double counting is trivial. Ideally, we need to *deduct* from the total the share of Industry direct regulatory costs which would be recovered in the lost sales revenue of delayed and non-marketed drugs. Expressing direct regulatory costs of £8m-16m as a share of Industry's total sales, suggests that we need to revise downwards the estimated total by £176,000 to £353,000 per annum!

54 Our simplifying assumptions result in estimates similar to the costs imposed on the Industry: see Table B4.

55 One firm in the survey stated that 'given that the costs of producing an NCE to the parent company are trivial compared with the final selling price, the loss to an individual firm approximates to the sales loss rather than profits loss'. Also, if the offsetting adverse effects on *existing* products are so small that they can be ignored, the estimated social costs will be greater (i.e. by the area P_1PA in Figure 1).

56 Assuming lost sales revenue due to delays of £36m; plus £10m of lost revenue due to drugs not marketed; plus direct regulatory costs of £19.7m. See Table B4 and estimates of direct social costs.

57 B. Cromie, Motoring and Medicine, *World Medicine,* Sept.22, 1979; also B. Cromie, Present Problems: The Effects of British Regulations, *Symposium on Medicines in the Year 2000,* OHE.

58 It is, of course, recognised that DHSS staff handle licensing applications for both human and animal medicinal products.

59 G. Teeling-Smith, *A Question of Balance: The Benefits and Risks of Pharmaceutical Innovation,* OHE, London; also M.E. Jarvik, Necessary Risks, *New England Journal of Medicine,* June 7, 1979. Surgery is a further example of a risky activity.

60 DHSS Medicines Commission, *Annual Report,* 1978, HMSO, London, HC 163, Appendix III, Product Liability.

61 R. Temple, *et al.* Adverse Effects of Newly Marketed Drugs, *New England Journal of Medicine,* May 3, 1979; also A.B. Wilson, *Registration of New Drugs and Post-Marketing Surveillance,* FIP Meeting, Cannes.

62 B.G. James, *The future of the multi-national pharmaceutical industry to 1990,* ABP Ltd., 1977, pp.102, 103, 148.

63 Medico-Pharmaceutical Forum, *Post-Marketing Surveillance of Adverse Reactions to New Medicines,* Publication No.7, December 1977.

64 One firm compared the costs of the non-clinical components of a Product Licence submission for 1965 and 1979 (development, drug metabolism and toxicology). Total R & D costs for a PL submission rose from £181,000 in 1965 to £585,000 in 1979, with regulation accounting for £88,000 of this increase (all in 1979 prices). Also, the firm's manpower involved in UK and overseas regulatory affairs rose from 25 in 1968 to 130 in 1979.

65 D. Schwartzman, *The Expected Return from Pharmaceutical Research,* American Enterprise Institute, Washington D.C., 1975.

66 OECD Sees Dangers in Over-Regulation of Pharmaceutical Industry, *Scrip,* No.525, September 17th, 1980, p.2; F. Steward and G. Wibberley, Drug Innovation: What's Slowing It Down? *Nature,* Vol.284, 13 March, 1980; R. Hansen, *The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes,* Center for the Study of Drug Development, Rochester, Reprint Series RS7923, June 1979.

67 Keith Hartley, Defence and Advanced Technology and A. Maynard, The Economics of Industrial Policy, both in D. Dosser, *et al.* (eds.), *The Collaboration of Nations,* Martin Robertson, 1982.

68 Chemicals EDC, *UK Chemicals 1975-85: Sector Group Report for Pharmaceuticals,* NEDO, January 1976, mimeo, Section 1.

69 A study of the UK Home Medicines Industry estimated that legislation, particularly the 1968 Medicines Act, had reduced the Industry's *expected* rate of return on innovative investment from 18.1% to 10%: W.D. Reekie, Legislative Change and Industrial Performance, *Scottish Journal of Political Economy,* June 1980, p.123.

70 W.D. Reekie, Legislative Change and Industrial Performance: A Case Study, *Scottish Journal of Political Economy,* June 1980, p.124. The Home Medicines Industry provides medicines which are available without prescription (e.g. cold remedies, laxatives).

71 Since this survey was undertaken, a clinical trial certificate exemption scheme has been introdued and is working well.

72 Merck & Co. has estimated that between 1968 and 1978, 69% of their new drugs were rejected after initial clinical testing. If the U.S. proposals for carcinogenicity tests had been performed on all these drugs, approximately $12m would have been wasted: *Scrip,* 407, July 28, 1979, p.10.

Appendix A

QUESTIONNAIRE: SUMMARY OF RESPONSES

Objectives

This questionnaire is concerned with pharmaceuticals for *HUMAN* use and its main objectives are as follows:

1 To assess the general effects of the 1968 Medicines Act, as seen by your company.

2 To obtain information on the costs of administering the 1968 Medicines Act.

3 To acquire information about the time interval between the date at which a new chemical entity (NCE) is synthesised and the date at which a product licence is issued.

Organisation

The questionnaire is divided into 3 parts:

(A) is a general questionnaire about the effects of UK Government regulation.

(B) is concerned with eliciting the costs of the 1968 Medicines Act.

(C) is a detailed questionnaire which requests precise information about products developed by your company in the 1964-1979 period.

Completing the questionnaire: Instructions

1 Please rank your answers where required. Otherwise tick or circle the correct response from the alternatives listed.

2 Generally, the questions refer to your firm's UK operations.

3 If you require additional space for an answer, please use the nearest blank side (i.e. reverse page).

GENERAL

1 Company

16 responses

2 Name and Position of Respondent(s)

Examples: **Head of Regulatory Affairs**
Group Secretary
Managing Director
Deputy Chairman

3 Date of Response

(i)March-Sept 1980
(ii)Revised: Final Version: June 1981

4 Characteristics of Company (please tick where appropriate):

(a) Is your company

(i) UK-owned	7
(ii) Foreign-owned	9

(b) Employment in the UK **55,147**

(c) Capital employed in the UK **£654.7m (n = 11)**

(d) In which nation is the Company's *main* R & D effort located?

UK	**7**
USA	**5**
Switzerland	**2**
W. Germany	**1**
Netherlands	**1**

Note: n shows the number of respondents—e.g. n = 11 represents 11 respondents to the question. The more respondents to a question, the greater is the reliability of the answer. For example, 15 firms agreeing on a reply represents a reliable generalisation.

SECTION A Effects of 1968 Medicines Act

1 What have been the major effects of the 1968 Medicines Act on your firm? Please *rank up to 5* in order of importance (1 = first, 2 = second, etc.):

		Rank	*Total number of responses**
(i)	Patients have benefited from improved safety.		**2 (0)**
(ii)	(a) Higher prices of drugs (b) If so, how much higher (in 1968 values)? _____%	**VI**	**6 (2)**
(iii)	(a) It takes longer to develop and market new drugs. (b) If so, how much longer? **20-300%**	**I**	**16 (13)**
(iv)	Fewer new drugs are marketed—i.e. less innovation.	**III**	**10 (1)**
(v)	(a) Less basic research and more spent on development. (b) If so, how much less basic research? **12-56%**	**II**	**12 (0)**
(vi)	(a) Compared with 1968-71, UK firms are undertaking more clinical R & D abroad. (b) If so 1. which R & D? **Clinical** 2. what percentage of annual R & D expenditure is now spent abroad? **20%** 3. in which countries? W. Germany **(n = 6)** Scandinavia **(n = 4)** Europe **(n = 4)** USA **(n = 3)**	**V**	**8 (1)**
(vii)	(a) Inefficiency in testing. (b) If so, do you mean that (please tick): 1. there is too much testing? **5** 2. tests are too costly (they could be done more cheaply)? **1** 3. innovation in testing has been retarded? **4** 4. the testing is ineffective? **3**	**VII**	**6 (0)**

(viii) (a) Loss of international competitiveness. **3 (0)**
(b) If so, in which overseas markets (specify)?
e.g. E. Europe
N. Africa
Syria

(ix) Act has reduced
(a) the import of inferior drugs. **2 (0)**
(b) the domestic manufacture of inferior drugs.

(x) Act has reduced
(a) the import of drugs which have been pirated or copied. **1 (0)**
(b) the domestic manufacture of drugs which have been copied. **1 (0)**

(xi) Greater use of outside research laboratories. **1 (0)**

(xii) (a) Firms are now more cost conscious in R & D; and **1 (0)**
(b) This has increased the productivity of R & D.

(xiii) Greater quality control in manufacturing. **3 (0)**

(xiv) Greater restrictions on advertising, information and packaging. **9 (0)**

(xv) Others (specify). **3 (0)**
e.g. (a) Higher capital expenditure in manufacturing and warehousing. **1 (0)**
(b) CRM involves extra work for Industry and discontinuation of some drugs. 1 (0)

Note: *Figures in brackets show number of firms giving a *first* rank to an answer—e.g. 13 firms gave a first rank to effect (iii).

2 If you were given *a maximum of 10 points* to be allocated amongst the 5 factors you have chosen in (1) above, how would you allocate these points (e.g. if you think all are equally important, then you would allocate 2 points to each; or, if 1 is overwhelmingly important, you might give it, say, 7 or 8 points).

Options by Rank		*Number of Points*
1	**Range:**	**3—5**
2		**2—4**
3		**1—2**
4		**1—2**
5		**1**
Total		**10**

3 To what extent has the 1968 Act *only* contributed to the effects outlined at (1) above (please tick):

(i) It explains *all* of the effects (100%) **0**

(ii) It explains most of the effects (50%-99%) **10**

(iii) It has made a moderate contribution (25%-49%) **5**

(iv) It has had a small effect (under 25%) **1**

(v) It has had no effect **0**

4 *R & D*

(a) Since 1968 has your firm's UK R & D expenditure increased/decreased/remained the same (in 1968 values). Please ring one.

Increased: 13
Decreased: 0
Same: 2

(b) (i) If expenditure has either increased or decreased, how much of the change is due to the 1968 Medicines Act *only* (please tick):
1. All of the change (100%) **0**
2. Largely (greater than 50%) **4**
3. Partly (25%-50%) **5**
4. Very little (under 25%) **4**

(ii) Where UK R & D expenditure has changed, is any of this affected by:
1. Regulation in rest of world? **Yes: 13**
No: 0
2. Technical progress **Yes: 12**
No: 1

(c) If UK R & D expenditure has increased, please indicate the major sources of higher spending (e.g. testing—which type—and percentage increase since 1968—in 1968 prices).
(i) Toxicology (n = 10) **100%—370%**
(ii) Clinical Studies (n = 7) **75%—400%**
(iii) Drug Metabolism (n = 3) **300%**

(d) Which items of UK R & D spending have risen *mostly* because of technical progress and the increasing complexity of R & D work?
(i) Drug Metabolism **(n = 4)**
(ii) Automation **(n = 4)**
(iii) Toxicology **(n = 3)**

(e) What percentage of your firm's UK R & D budget is spent on work sub-contracted to outside research agencies—laboratories? **0.5—80% (n = 13)**

(f) Has the percentage of outside research contracting risen in the last 10 years? **Yes: 8**
No: 5

(g) If YES, does the 1968 Medicines Act account for this rise:
(i) Wholly (100%) **0**
(ii) Largely (over 50%) **2**
(iii) Partly (25%-50%) **5**
(iv) Very little (under 25%) **1**

(h) For a typical drug, what is the time period and cost between:

	Time	*Cost (1979 prices)*
(i) Patenting of new chemical entity and first clinical trial certificate?	**2 yrs—12 yrs**	**0.4m—20m**
(ii) Patenting NCE to market launch?	**5 yrs—15 yrs**	**1.5m—30m**

(i) Without the 1968 Medicines Act, what would be the time period and costs for the typical drug described at (h) above:

	Time	*Cost (1979 prices)*
(i) Patenting of NCE to clinical trials?	**1 yr —10 yrs**	**0.3m—20m**
(ii) Patenting to market launch?	**2⅓ yrs—12 yrs**	**1m —23m**

(j) What proportion of your firm's total R & D was undertaken in the UK in 1968 compared with 1979?
1968: **0.5—100%**
1979: **1.5—100%** **(n = 11)**

(k) What was your firm's UK R & D expenditure as a percentage of your total UK sales (i.e. home and export) in?
1968: **3.8—33%**
1979: **3.8—20%** **(n = 11)**

(l) (i) Has the 1968 Act biased R & D programmes towards certain types of drugs? **Yes: 6** **No: 8**

(ii) If so, which types and why?

(m) (i) Would you enter UK based R & D today? **Yes: 11** **No: 3**

(ii) If NO, why not?

5 *Exports*

(a) Have your exports (in volume) increased/decreased/remained unchanged since the 1968 Medicines Act (please ring one)?
Increased: 13
Decreased: 0
Same: 2

(b) If exports have changed, how much of the change, if any, is due to the 1968 Medicines Act?
(i) Wholly (100%) **0**
(ii) Largely (over 50%) **0**
(iii) Partly (25%-50%) **0**
(iv) Very little (under 25%) **12**

(c) Are export prices higher/lower/same as the UK prices of drugs (please ring one)? **Higher: 8** **Lower: 0** **Same: 3**

(d) If export prices are higher/lower, please explain why:
(i) Higher/lower costs and risks of export business **6**
(ii) Less/more overseas competition **3**
(iii) UK 1968 Medicines Act has raised costs of selling in the UK market **2**
(iv) Others (specify) **4**

(e) Are exports more profitable/less profitable/as profitable as home sales (please ring one)?
More: 7
Less: 1
Same: 3

(f) If exports are more profitable, please explain why:
(i) Absence of UK regulatory requirements **1**
(ii) Presence of UK price restrictions **6**
(iii) Unique product with no rivals **—**
(iv) Others (please specify)

(g) (i) Has your firm established local (foreign) processing facilities as a result of the 1968 Act? **Yes: 0** **No: 15**

(ii) If so, what has been the magnitude of your overseas investment (1979 values)?

6 *Quality Control*

(a) What was your firm's expenditure on quality control as a percentage of total sales in:
1968: **0.3—10.6%**
1979: **0.5— 7.3%** **(n = 11)**

(b) Has the 1968 Act improved quality control in manufacturing? **Yes: 10** **No: 4**

(c) What have been the *extra* costs (capital and production costs) to your firm of any improved quality control (1979 values)? **£150,000—£7m (n = 7)**

(d) As a result of the quality changes due to the 1968 Act has patient safety improved? **Yes: 6** **No: 8**

(e) In the absence of the 1968 Act would your firm have introduced any additional quality controls? **Yes: 13** **No: 1**

(f) Would the costs of such voluntary improvements in quality control (1979 values) have been higher /lower/the same as the costs required due to the 1968 Act (please ring one)? **Higher: 1** **Lower: 6** **Same: 7**

(g) Would your company's proposed voluntary changes on quality control have resulted in a higher/lower /unchanged level of patient safety compared with the current situation (please ring one)? **Higher: 1** **Lower: 0** **Same: 11**

7 *Advertising*

(a) What was your firm's advertising, information, packaging and merchandising expenditure (i.e. selling costs) as a percentage of total sales in:
1968: **5 —15%**
1979: **5.1—18.7%** **(n = 12)**

(b) (i) Has the 1968 Act resulted in any changes in your firm's advertising, information, packaging and merchandising policies: **Yes: 11** **No: 4**

(ii) If YES, please specify major changes, with examples:
1. Data sheets **(n = 7)**
2. Labelling **(n = 4)**
3. Child proof packs **(n = 3)**

(c) (i) Have the changes listed at (b) above resulted in higher selling costs for your firm? **Yes: 8** **No: 4**

(ii) If YES, how much higher (in 1979 values only)? **1—10% (n = 2)**

(d) Have the advertising, etc. changes due to the 1968 Act resulted in a higher/lower/unchanged *volume* of sales (please ring one)? **Higher: 0** **Lower: 2** **Same: 10**

8 *Licensing Authority*

(a) How long does the licensing authority take to handle your application for a:
(i) CTC **4m—18m**
(ii) Product licence **3m—20m** **(n = 16)**

(b) Has the period at (i) above (CTC) increased/decreased/remained the same over the last 10 years (please ring one)? **Increased: 14** **Decreased: 1** **Same: 1**

(c) Has the period at (ii) above (PL) increased/decreased/remained the same over the last 10 years (please ring one)? **Increased: 14** **Decreased: 0** **Same: 2**

(d) If either or both have increased, has the rise been due to (please *rank the first 5* in importance; 1 = most important, etc.):

		*Rank**	*Number of responses*
(i)	Greater complexity of technology and hence more complex applications.	III	15
(ii)	Increased number of applications to be handled by the licensing authority.	IV	12
(iii)	Shortage of qualified licensing authority staff.	I	15
(iv)	Increased regulatory requirements.	II	15
(v)	Greater concern with public safety.	V	8
(vi)	Firm being unwilling to accept limitations which licensing authority wishes to impose on the licence.		3
(vii)	Firm failed to reply to correspondence from licensing authority.		0
(viii)	Firms more willing to appeal against licensing authority decisions.		4
(ix)	Others (specify).		3
	1. Increasing bureaucracy	**(n = 1)**	
	2. Legal framework	**(n = 1)**	

Note: *Ranked by number of responses and priority (i.e. number of 1st ranks). There were seven firsts for (iii), five for (iv) and none for (i).

(e) Take the *single,* most important factor listed in (d) above (i.e. rank = 1). How much does this one factor explain the increased time:

(i)	Wholly (100%)	2
(ii)	Largely (50%-99%)	10
(iii)	Partly (under 25%)	3

(f) 1. Has the licensing authority ever refused to award your firm a licence for a:

(i)	CTC	**Yes: 2**
		No: 14
(ii)	Product licence	**Yes: 7**
		No: 9

2. If YES to (f) give percentage of applications rejected (1-15%) and reasons for rejection:

(i)	Considered to be unsafe	2
(ii)	Errors in testing	0
(iii)	Failed to conform to testing and documentation requirements	2
(iv)	A completely new drug (major innovation) which was believed to be too risky without further testing	1
(v)	Withdrawn	5
(vi)	Others (specify)	2

(g) (i) Has your company ever withdrawn an application to the licensing authority? **Yes: 13** **No: 3**

(ii) If YES, give brief details of the application and reasons for withdrawl.

1. Extra data, etc. required **(n = 7)**
2. Adverse reactions **(n = 3)**

(iii) Has your company ever delayed the marketing of a new drug *after* receiving a Product Licence? **Yes: 11** **No: 4**

(iv) If YES, please explain why.

1. Commercial reasons **(n = 7)**

(h) On average, how many pages of documentation are submitted for:

		NCE	*Non-NCE*
(i)	a CTC	**600—3,000**	**20—5,000**
(ii)	a Product Licence	**300—5,000**	**50—5,000**

(n = 15)

(i) Has the number of pages of documentation at (h) above increased/decreased/remained the same since licensing was enforced in 1971 (please ring one)? **Increased: 15**

(j) Where the number of pages of documentation has risen, please indicate the approximate percentage increase since your first application was submitted. **10—1,000% (n = 15)**

(k) (i) Is the DHSS faster than any other nation at handling licensing applications? **Yes: 5** **No: 10**

(ii) If NO, which nations are faster and by how much? **Eire (n = 8)**

9 *Likely effects from the Abolition of the 1968 Medicines Act*

(a) How would *your firm* respond to the abolition of the 1968 Medicines Act. *Rank up to 5* in order of importance:

		*Rank**	*Number of responses*
(i)	Basic research would increase/decrease/remain the same (please ring one).	III	9
(ii)	Development work would increase/decrease/remain the same (please ring one).	IV	8
(iii)	Prices of drugs would fall.		0
(iv)	(a) Employment would fall.		3
	(b) If so, which categories of labour?		—
(v)	Less R & D overseas and more in the UK.	II	9
(vi)	More new drugs would be marketed.	I	11
(vii)	More advertising.		2
(viii)	Increased exports.		4
(ix)	Less testing.	V	6
(x)	(a) Different types of testing would take place.	VI	5
	(b) If so, please explain and specify.	—	
(xi)	Others (please specify).		4
	1. Earlier clinical trials	**(n = 1)**	
	2. Greater profits before patent expiry	**(n = 1).**	

Note: *Ranked by number of responses and priority. There were 6 firsts for (vi), 3 firsts for (v) and 1 first for (i).

(b) If the 1968 Medicines Act were abolished, which types of testing would you:

		All	*Most*	*None*
(i)	Retain (specify)	6	6	
(ii)	Abandon (specify)	0		5
(iii)	Postpone until later in the development process (specify)			Yes: 11
	1. Fertility		(n = 6)	
	2. Long-term		(n = 6)	

(c) If the 1968 Act were abolished, would the costs of testing rise/fall/remain unchanged (please ring one)?

Rise: 0
Fall: 9
Same: 4

(d) (i) Has safety improved as a result of the 1968 Act? **Yes: 8** **No: 5**

(ii) If YES, please explain.
1. Eliminated unsafe products.
2. Improved testing in less reputable firms.

(e) (i) What beneficial effects has the Act had on patients?
None: (n = 7)
Some: (n = 8)

(ii) What harmful effects has the Act had on patients?
1. Delayed introduction of new drugs **(n = 14)**

10 *Future Policy*

(a) Should the 1968 Medicines Act be (please tick one):
(i) Retained in its present form? —
(ii) Modified? **16**
(iii) Abolished? —

(b) Please explain your choice at (a) above (ranking your replies in order of importance).

		*Rank**	*Number of responses*
(i)	Act has been beneficial (to whom?)		4
(ii)	Act has had net adverse effects on the pharmaceutical industry.	II	13
(iii)	Act has had net adverse effects on patients.	III	11
(iv)	The Act is too bureaucratic—i.e. rigid, inflexible, slow, delays.	I	15
(c)	Others (specify).		2

Note: *Eleven firms gave a first rank to (iv); two firms gave a first rank to (ii).

(c) If you prefer the Act to be MODIFIED, please list and rank the major modifications. (1 = most important, etc.)

	Rank	*Number of responses*
1. More flexibility	I	12
2. Fewer delays, etc.	II	6

(d) If you would like the Act to be ABOLISHED, what is your preferred regulatory system:
(i) None—i.e. no state intervention —
(ii) Industry to regulate itself—specify how, why and who would benefit? —
(iii) Adopt another country's approach—which country, why and who would benefit? —
(iv) Other (specify).

SECTION B Costs of the 1968 Medicines Act

1a) Has employment in your firm since the 1968 Act decreased/increased/remained unchanged (please ring one)?

Increased: 13
Decreased: 1
Same: 1

(b) Please identify the main categories which have either changed or remain unchanged (tick where appropriate):

		Increase	*Decrease*	*No Change*
(i)	Legal and administrative staff (e.g. with the word registration or regulatory in their job titles)	14	0	1
(ii)	Number employed on testing	13	0	1
(iii)	Others (specify)	6	1	

(c) If employment in your firm has *increased* as a result of the 1968 Act, please estimate by how much numbers have risen (full-time equivalents):

		Extra Employment Per Firm
(i)	Legal-administrative	**range: 1—30**
(ii)	Testing	**5—50**
(iii)	Others	**2—50**

(d) To what extent does the 1968 Act *only* explain the increased employment estimated at (c) above (please tick one):
(i) Wholly (100%) 2
(ii) Largely (50%-99%) 3
(iii) Moderately (25%-49%) 6
(iv) Very little (under 25%) 4

(e) If other influences have contributed to the higher employment estimated at (c) above, please list which 'others':
1. Overseas regulation **(n = 6)**
2. Greater R & D **(n = 6)**
3. Greater sales **(n = 5)**

(f) How many extra staff (full-time equivalents) are due to international regulatory requirements rather than UK regulatory requirements? **range: 2—100**

2. What is the current average wage or salary of a full-time equivalent employee in:

(i)	Legal-administration work	**£4,500—11,000 (n = 12)**
(ii)	Testing	**£4,000— 8,500 (n = 12)**
(iii)	Other	**£3,500— 8,000 (n = 8)**

3 What were your firm's total UK costs of production in 1979 (i.e. excluding profits)? **£11m—135.1m (n = 7)**

4 How long does it take to prepare (i.e. assembly of materials *after* testing) the documents for submission for: **(n = 14)**

		NCE	*Non-NCE*
(i)	CTC	**3wks—6m**	**3wks—6m**
(ii)	Product Licence	**2m —9m**	**1wk —6m**

5 What are the total costs (salary and overheads, materials, etc.) of preparing the submission at (4) above for: **(n = 10)**

		NCE	*Non-NCE*
(i)	CTC	**£2,000— 50,000**	**£740—25,000**
(ii)	Product Licence	**£2,000—100,000**	**£500—50,000**

6a) Has the 1968 Act delayed marketing (due to testing and licence application delays)? **Yes: 15**
No: 0

(b) If YES, what is the average length of this delay (i.e. due to testing and application process)?
range: 1yr—5yrs (n = 14)

(c) If YES to (a) above, and *for an average product,* what are the total costs of the delays (1979 values) in the form of:
(i) Lost sales revenue per product **range: £1m—20m**
(ii) Lost profits per product **£100,000—15m**

SECTION C Time Lags between Synthesis and Marketing of NCEs

(A) General Instructions

1 Our interest is in NCEs for humans which were tested or marketed in the UK between 1st January, 1964 and 1st January, 1979.

2 We would like you to select FIVE (5) NCEs in the following way:

(i) take the alphabetical list of your products, as listed in the ABPI's Data Sheet Compendium 1979-80, and supply the information requested on the third (3) and eleventh (11) items in this list.

(ii) select ANOTHER TWO (2) products, one from the period prior to 1968 and one from the period 1974-79, and supply the information requested, noting briefly the reasons for your selection.

(iii) provide the information requested for ONE MORE (1) product from your list, noting briefly the reasons for your selection.

3 NCE = New Chemical Entity, i.e. a compound with a molecular structure which has not been *tested* or *marketed* previously. Please exclude new salts, esters and new dosage forms of existing compounds *unless* they give distinctive medical benefits, and any compounds tested prior to 1st January 1964. Please include biologicals, vaccines and diagnostics. Please include any NCE which you have doubts about and give us a brief explanation of the causes of your doubts.

(B) Specific Instructions

Questions 1-4 are self-explanatory.

Question 5: the generic name will enable us to identify any drug licensed by several different companies.

Questions 6-14 are self-explanatory.

SECTION C

Time Lags between Synthesis and Marketing of NCEs

	DRUGS				
	1	*2*	*3*	*4*	*5*
1. Therapeutic class					
2. Source of this new compound (specify date of patent) (i) invented by this company (ii) licensed (iii) other					
3. If answer to (2) is (ii) or (iii) specify: (i) company (ii) country					
4. Please give *country* and date of the following events in the NCEs development: (i) chemical synthesis (ii) start of pharmacologic definition process (e.g. administration to animals etc.) (iii) first administration to human subjects (volunteers) (iv) first administration to patients (v) first marketing (vi) date of marketing in UK (vii) rank order of UK marketing (e.g. enter 3 if the UK was the third market in which this drug was sold)					
5. Brand and generic name (see instructions) of UK product					
6. Date of application for *initial* CTC. (If no CTC application has been made yet, insert NA) (month and year)					
7. Date of CTC approval (letter of intent) (month and year)					
8. Date of application for PL (if no application has been made yet, insert NA) (month and year)					
9. Date of PL approval (letter of intent) (month and year)					
10. Date of PL approval (receipt of formal documents) (month and year)					
11. Indications approved by PL procedure: (i) first product licence (ii) subsequent PL procedures					
12. If PL is still pending, is it still active?					
13. If PL not approved and not active, give date of abandonment (month and year)					
14. If approved outside UK, name of: (i) first country (ii) first country amongst highly regulated nations (iii) trade name in that country (iv) date of approval in that first country					

GENERAL INFORMATION: Please complete the following, 1960-1979

Year	*Employment (full-time equivalents)*						*Total value of UK output £m*	*Total exports from UK £m*	*UK R & D spending £m*
	Legal-administrative personnel	*Testing Personnel*				*Total employment in company*			
		Chemistry-pharmacy	*Pre-clinical*	*Clinical*	*Other testing*				
1960									
1961									
1962									
1963									
1964									
1965									
1966									
1967									
1968									
1969									
1970									
1971									
1972									
1973									
1974									
1975									
1976									
1977									
1978									
1979									

Appendix B

STATISTICAL ANALYSIS: A STUDY OF FIRMS

1 The aims of the statistical study

A statistical analysis of firms was undertaken to:

(a) Test for any significant impact of the 1968 Act on employment, exports, and R & D at the firm level.

(b) Estimate the *quantitative* impact of the Act on individual firms.

(c) Check the validity of firms' responses to the questionnaire.

2 The sample

2.1 Firms in the sample were asked for annual data on their *UK* employment, output, exports and R & D spending for 1960-79.

2.2 Only six firms provided data suitable for statistical analysis, although it was not always possible to satisfy all our detailed requirements.

2.3 The six firms, 4 UK-owned and 2 foreign-owned, employed a total of 24,124 employees in 1979.

2.4 With such limited data, the statistical results should be regarded as no more than tentative and exploratory.

3 The model

3.1 The possible impact of the 1968 Act was estimated by incorporating a dummy variable into multiple regression equations. A dummy variable distinguishes between 'before' and 'after', *ceteris paribus*—i.e. it estimates for 'no effect' before the Act and a 'once-and-for-all effect' afterwards.

3.2 In using a dummy variable, there are questions about the effective starting date for the Medicines Act. Two possibilities were tested:

(a) A 1968 starting date
(b) A 1971 starting date.

3.3 To hold constant 'other relevant influences', the dummy variable was incorporated into general estimating equations. Output and a time-trend were used to represent 'other factors'. Thus, the general models formulated to test for the effects of the 1968 Act were:[1]

(a) $N = N(Q, DV, t)$
(b) $X = X(Q, DV, t)$
(c) $RD = R(Q, DV, t)$

where N = employment (numbers) in a firm measured by totals and sub-group where data were available.
Q = value of a firm's output (£m)
DV = dummy variable (0.1) for the 1968 Act
t = time-trend
X = value of a firm's exports (£m)
RD = firm's research and development expenditure (£m).

3.4 It was predicted that the dummy variable for the 1968 Act would have positive effects on employment and R & D, and a negative effect on exports—i.e. increases in employment and R & D spending, and a decline in exports following the 1968 Act. However, it is recognised that the predicted effects of the 1968 Act might be ambiguous. For example, if the Act has made the UK less attractive for R & D, there might be a negative effect (i.e. less) on R & D spending; and this might be reflected in lower employment, especially for R & D staff (i.e. a negative effect).

3.5 Output was expected to have a positive impact on employment and on R & D. Either positive or negative relationships are plausible between output and exports, depending on a firm's cost conditions.[2]

3.6 Each of the general estimating equations was modified. Some employment equations included both current and the previous year's output. Elsewhere, R & D spending was substituted for output: it was felt that R & D might be a more accurate determinant of some types of employment (e.g. clinical). Also, in the export and R & D equations, both levels and shares in a firm's total output were used as dependent variables.

4 Limitations of the results

Three limitations have to be stressed:

(a) The relatively small data set for each firm means that the results are tentative, limited and suggestive.

(b) Definitions might not be comparable between firms. For example, firms may have used different definitions for R & D spending and other testing staff. Detailed checking of this aspect of our work was limited by resource constraints.

(c) The individual features and peculiarities of each company might not be captured by our general estimating equations.

5 A guide to interpreting the results

Interesting results are represented by:

(a) Significant coefficients. These are shown by either ** or *, indicating a very reliable or a quite reliable result, respectively, from the point of view of conventional statistical tests (i.e. at the 1% or 5% levels of significance). With significant coefficients, we are interested in their *sign* (positive or negative) and *size*.

(b) The amount of explanation offered by an equation. This is shown by R^2. For example, an R^2 of 0.95 means that 95% of the variation in, say, employment (N) is 'explained' by the variables in the equation.

(c) The Durbin-Watson statistic. This is a further indicator of reliability (i.e. autocorrelation or related error terms). It is represented by DW, with a value in the region of 2 indicating a reliable result from the conventional statistical viewpoint.

6 Examples of the results

Only three firms provided a data set with sufficient observations 'before and after' the 1968 Act. Examples of the results are shown in Table 1,[3] where it can be seen that the equations gave 'reasonably good fits'. The limitations of the results, arising from the sample size and the constraints on the specification of the variables, must be stressed.

TABLE 1

Dependent variable	Coefficients of: Constant	Q	log Q	RD	Dummy (1)	Dummy (2)	t	$\bar{R}^2$	DW
Firm 1L									
1. LAP	6.55†	-0.35			-4.27*		1.92*	0.68	1.72
	(1.87)	(0.27)			(1.95)		(0.84)		
2. TEC	8388.19†	57.84				-313.66	37.23	0.85	1.80
	(229.43)	(38.71)				(302.92)	(109.11)		
Firm 2M									
3. LAP	8.37†	0.08			4.12†		-0.02	0.86	2.37
	(0.74)	(0.06)			(1.56)		(0.18)		
4. TEC	695.67†	-7.48			615.08†		187.96†	0.98	0.61
	(80.48)	(6.38)			(170.26)		(19.95)		
5. X	-3.16†	0.91†			-4.82*		-0.51	0.98	0.63
	(1.00)	(0.08)			(2.12)		(0.25)		
6. X	-0.42	0.64†				8.10†	-0.56†	0.99	1.73
	(0.69)	(0.05)				(1.31)	(0.15)		
7. log RD	0.18		0.24*		0.55†		0.03	0.94	1.88
	(0.13)		(0.08)		(0.15)		(0.02)		
Firm 3M									
8. TEC	1268.51†			53.35	-276.11*		146.34†	0.98	1.32
	(101.59)			(34.35)	(112.99)		(19.01)		
9. RD	2.85†	-0.005				2.03*	0.42*	0.94	2.31
	(0.44)	(0.029)				(0.74)	(0.15)		

Notes: (i) LAP = numbers employed of legal and administrative personnel; TEC = total employment in the company. Firm 1L was a large firm with over 5,000 employees. Firms 2M and 3M were medium size units, with employment of 2,000-5,000.

(ii) Q = total value of company's UK output (£m, 1975 prices).

(iii) X = company's total exports from UK (£m, 1975 prices).

(iv) RD = company's research and development expenditure (£m, 1975 prices).

(v) Dummy (1) = dummy variable for the 1968 Act: 0 = 1960-67; 1 = 1968-78.

(vi) Dummy (2) = dummy variable for the 1968 Act: 0 = 1960-70; 1 = 1971-78.

(vii) t = time-trend. Firm 1L, t = 1966-78; firms 2M and 3M, t = 1960-78.

(viii) $\bar{R}^2$ ± is adjusted for degrees of freedom; DW is Durbin-Watson statistic, which shows positive serial correlation in equations 4 and 5. Standard errors are shown in brackets, with some figures rounded to the nearest decimal place. † is significant at the 1% level; * is significant at the 5% level.

The main results from Table 1 can be summarised:

(a) *Employment.* The Act has been associated with positive, negative and non-significant employment effects! Firm 2 gave the expected results, showing the 1968 Act associated with a *positive* impact on legal and total employment (equations 3 and 4). However, the estimated increase of some 600 in total employment in firm 2 (equation 4) is only tentative, since the equation's reliability is affected by serial correlation. Interestingly, all firms showed evidence of a positive time-trend, indicating *rising employment over time.* If firms are unaware of the magnitude of such trends, it could lend them to over-estimate the employment effects of the 1968 Act, as reflected in their questionnaire responses. Nonetheless, all the employment equations were suspect in view of the failure to obtain significant coefficients for the output variable.

(b) *Exports.* The Act has been associated with ambiguous effects on exports. Firm 2 seemed to provide evidence of the expected negative impact (equation 5). But, serial correlation affected the reliability of the results and the sign became *positive* when dummy (2) was used (equation 6)! Elsewhere, the effect of the Act on export *shares* was either positive or non-significant.

(c) *Research and development.* There was substantial support for the predicted positive effect of regulation on the *level* of R & D spending. For firm 3, the result has been an increase in R & D spending of some £2.0m per year (1975 prices).

7 A comparision of the statistical and questionnaire results

7.1 There are significant discrepancies between the econometric and questionnaire evidence, with the latter showing that the 1968 Act has resulted in *higher* employment (an extra 500 staff: see Part II). Accurate comparisons are possible by analysing the questionnaire results of the six firms subjected to the econometric analysis, as shown in Table 2.

7.2 Various explanations can be offered for the discrepancies in the estimated *employment* effects:

(a) Data limitations: only 6 companies provided data suitable for econometric analysis and there was a relatively small data set for each firm (e.g. data were not always available for all categories of employment).

(b) Re-classification: organisational changes often lead to the re-classification of staff, so affecting the reliability of data on different sub-groups of employment (e.g. legal, administrative, testing, others). However, this should be less of a problem for total employment data.

(c) Limitations of the econometric equation: in particular, major reservations arise because output appears to have no statistically significant effect on total employment.

TABLE 2
Employment Effects of 1968 Act

Employment	*Company* 1	2	3	4	5	6
Econometric results:	Negative	Positive	Negative	No significant effect	No significant effect	No significant effect
Questionnaire results:						
(i) Increased employment due to the Act	Yes	Yes	Yes	Yes	Yes	Yes
(ii) Magnitude of any increase	5	76	16	73	14	14
(iii) Contribution of Act	Little	Little	Largely	Largely	Wholly	Moderate

Notes: *(i) Positive means higher employment.*
(ii) Companies 1-3 are as in Table 1. The econometric results for companies 4-6 were based on a more limited set of observations, hence their unreliability.

(d) The questionnaire evidence indicates that the employment effects of the 1968 Act are relatively small. For the 6 companies, the maximum increase in employment was less than 1% of their total labour force (an extra 198 staff: Table 2) with some 50% of this increase due to the 1968 Act! Such small magnitudes could be a major reason why the econometric results are so limited and unreliable. *At the same time, the relatively small magnitudes suggested by the questionnaire could be an indicator of their reliability* (i.e. biased replies would tend to exaggerate the employment effects of the Act). In this context, it is interesting to compare the statistical and questionnaire results for company 2: the former estimated that the Act had raised total employment by some 600 staff (Table 1), whilst the firm's questionnaire replies suggested an increase of 76, with the Act accounting for 'very little' of the increase!

7.3 A similar comparison of statistical and questionnaire results for the 6 companies and the effects of the Act on the level of *R & D* is shown in Table 3. Both sets of results point in the same direction of higher R & D spending attributable to the Act, although the questionnaire replies suggest only a limited impact.

8 Conclusion

This section should be regarded as an exploratory contribution designed to show the possibilities, limitations and problems of a detasiled statistical analysis of a limited set of firm-level data. Despite their limitations, the econometric results have provided a useful 'check' on the questionnaire replies. As a result, we feel more confident about the reliability of the questionnaire evidence.

1 The equations were constrained by the available data, both in terms of variables and the limited number of observations: hence, the *ad hoc* nature of the export and R & D models (e.g. no price variables in the export equations). The employment equations were derived from a standard employment function, without the lagged dependent variable. See K. Hartley and W. Corcoran, Short-Run Employment Functions and Defence Contracts, *Applied Economics*, Dec. 1975.

2 R. Cooper, K. Hartley and C. Harvey, *Export Performance and the Pressure of Demand*, Allen and Unwin, London, 1970.

3 The equations were estimated in both linear and log-linear forms, using ordinary least squares techniques and, where appropriate, Cochrane-Orcutt iterative techniques. The remaining firms only provided data for 1970-78.

TABLE 3
Effects of 1968 Act on R & D

R & D	*Company* 1	2	3	4	5	6
Econometric results:	Positive	Positive	Positive	No significant effect	NA	NA
Questionnaire results:						
(i) Increased R & D due to Act	Yes	Yes	Yes	Yes	Yes	Yes
(ii) Contribution of Act	Very little	Partly	Very little	Very little	Very little	Partly

Note: NA = no data provided.