THE INTERNATIONAL DIFFUSION OF PHARMACEUTICALS

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THE INTERNATIONAL DIFFUSION OF PHARMACEUTICALS

This book studies the factors that influence the rate at which pharmaceuticals spread around the world. A sample of 192 drugs and 18 countries is used over the time period 1954 to 1978. Emphasis is given to the impact of regulation on the international diffusion process. An appraisal of the regulatory stringency of the 18 nations is compiled via questionnaire responses from drug companies. These tightness ratings are then used to determine the impact on the timing of drug introductions. A desynchronisation effect is identified in that marketing dates do not follow a commercial pattern. It also emerges that regulatory stringency is wealth related, with the better off nations tending to have the tightest appraisal procedures. A diversion of interest to the less well-off countries is perhaps a consequence with a move to relatively early introductions in the later portion of the sample period.

The time difference between the introduction of drugs in the originating country and elsewhere declines markedly throughout study period. This is rather surprising during what has been a time of increasing regulatory stringency. An even more surprising result is the apparent constancy of the *total* time taken for drugs to spread between nations. It would seem that the pharmaceutical companies may have compensated for a tougher regulatory atmosphere in a number of ways. These may include adopting a multinational form of organisation, a prompter overseas application strategy, and a diversion of interest towards the less stringent nations. There are indications that regulation clearance intervals rise during the period, but this does not seem to add to the total time taken to market drugs. Compensatory action by companies seems to have been successful in containing the impact of a less hospitable environment.

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Note to Readers

For the convenience of readers *summaries* have been provided at the end of each chapter. They are a compressed version of the content of each chapter and are intended to help those in a hurry acquire familiarity with the general content of the book.

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1 Spatial Diffusion

INTRODUCTION

This study is concerned with the spread of pharmaceuticals between countries. In the jargon of economics, the topic is the spatial diffusion of pharmaceuticals. The purpose is to identify the major factors influencing the time taken for drugs to spread around the world. Delay in the arrival of pharmaceuticals, especially those involving major therapeutic advance, is a cause for concern. The non-appearance or long-deferred arrival of new treatments may have a marked impact on the human and material welfare of an economy.[1] The interest stimulated by the 'drug lag'[2] studies investigating the comparative performance of the USA and UK in the introduction of new pharmaceuticals, is indicative of a concern for greater understanding of the mechanisms of spatial diffusion. The present study is an attempt to add to knowledge of the process.

DETERMINANTS

Factors likely to influence the rate of spatial diffusion of pharmaceuticals are set out in schematic fashion in Figure 1.1. Arrival time lag refers to the time difference between the original release in the country of first marketing, and the release in particular destination countries. Arrival time lag may of course refer to one drug, to a mean of a sample of drugs, or to a mean value for a particular country.

INTRODUCTION DATE

The introduction date of a drug may be relevant to its rate of spread to other countries. Improved communications, and greater pharmacological awareness, reflecting heightened international concern to generalise the benefits of discoveries, are the type of influences that may

ARRIVAL
TIME = f ($I, RT, T, S, D, F, P, K, C$)
LAG

I = Introduction date of drug
RT = Regulatory tightness of countries
T = Therapeutic step
S = Attractiveness of markets
D = Type of country

. . . . . .

F = Type of firm e.g. multinational, not multinational
P = Patenting conditions
K = Type of drug
C = Currency, investment, and tax environment

Note No information has been collected in this study on the items listed below the dotted line.

FIGURE 1.1 *Possible influences on spatial diffusion rates*

accelerate the spatial diffusion of many recently released drugs. Anticipating the results of this study, there is evidence to suggest that for more recent pharmaceuticals the time interval between original introduction dates and subsequent release in other countries, has declined markedly throughout the 1954 to 1978 time period. Interpretation of this result however requires care. Measurement of arrival time lags is based on first marketing dates in destination countries. No evidence is available on pre-release time intervals during which regulatory screening takes place.[3] This is a major disadvantage which is explained at greater length in the next chapter.

REGULATION

Regulatory stringency or tightness is likely to be a major influence on the rate of international spread of pharmaceuticals. Companies must comply with registration requirements and obtain clearance before marketing of a drug may commence. Obtaining permission to make a pharmaceutical available for sale may be a lengthy process. The regulatory phase may therefore be a considerable influence on the timing of the diffusion process. Countries vary widely in their attitude towards new pharmaceuticals. Some regulatory systems adopt a highly trusting

attitude towards applicant companies. The administrators behave like joint venture partners in the process of innovation. The impetus is towards securing pharmaceutical advance. Other systems are completely different in character. They are mistrustful of applicant companies, and often reflect a consumer protection attitude. The emphasis is to protect the public from 'bad' drugs, not to hasten the relief of illness and disease. Under these circumstances delay in processing applications is not deemed to be a major cause for concern by the regulators. In a protection orientated organisation, delay creates the impression of meticulous appraisal and acute concern for the public well-being. Other things being equal, countries with trusting regulatory systems are likely to be prompt in their appraisal of new pharmaceuticals. Mistrustful systems on the other hand are likely to be stringent in their attitude and lengthy in their deliberations. Delay is therefore likely to be considerable.

Companies can take some steps to counter regulatory delay. They can give absolute priority to achieving speedy clearance. Requests for classification, additional information and supplementary data, can all be supplied to the regulators with the minimum of delay. Application strategy between countries can also be relevant. A change from sequential applications, where acceptance in one country then leads to application in another, can be replaced by a greater degree of simultaneity. A new drug can be submitted to a large number of nations over a short period of time. In this way the time difference between clearances may be reduced. Since the early 1960s regulation has become much more rigorous. However the typical interval between the original marketing of drugs and their appearance for sale in the sample of countries used here, has declined quite dramatically. It is the author's hunch that a significant proportion of this reduction in diffusion lag, is due to a change in company application strategy. In order to compensate for increasingly tough and delaying regulatory procedures, companies may have bunched their submissions. In this way they may at least reduce the delay which is within their control. A change from sequential to simultaneous applications is thus a plausible explanation for the decline in diffusion time lags observed here. At a late stage in the preparation of this book some evidence became available on application dates. This is summarised in Chapter 7 where various tests are devised to identify types of application policy. Another plausible explanation is the increased multinationalism of drug companies is another. With widened geographical coverage, co-ordinated applications in many countries is probably made much easier. Unfortunately no evidence has been

collected on the multinationality of companies. The author's previous experience of the difficulty of the exercise induced caution.[4]

A number of companies have been approached and their Registration Managers asked to classify countries by the 'tightness' of their regulatory systems. A questionnaire has been used for the purpose. The responses allow an overall classification into categories of stringency ranging over a five point scale from the tightest to the loosest systems. Tests are then conducted to determine the influence of countries' registration procedures on the speed of diffusion of drugs. Some rather unexpected results have been found. They suggest that there is unlikely to be any simple relationship between the tightness of regulation and the arrival time lag of drugs. The expectation that countries with the most stringent procedures will have the slowest diffusion times is not supported. A rather more complex relationship is suggested which may involve either a risk aversion explanation and/or an adjustment mechanism between market size and regulatory attitudes.

THERAPEUTIC STEP

The importance of a drug is likely to be a major factor influencing its rate of global diffusion. Knowledge of dramatic therapeutic advances will spread quickly amongst the medical community. Adoption is therefore likely to be rapid. The Salk vaccine is a case in point. Poliomyelitis is a crippling disease. The development of an highly effective preventative vaccine was a major break through which met with an immediate response from doctors. Diffusion was extremely fast both within and between countries. Generalising from this example, it is not unreasonable to expect that drugs which incorporate really significant therapeutic advances, will spread rapidly around the world. Plausible though this expectation is, the evidence assembled here suggests that this is not the case. Apparently the importance of a drug is not a major factor influencing the rate of spatial diffusion. Something appears to be in operation which frustrates the expected relationship. Regulation may well be the culprit. Large and important therapeutic advances may well induce caution amongst those administering regulatory processes, and therefore lengthy appraisal may result. Relatively unimportant drugs may be equally delayed, not by the difficulty and/or novelty of the pharmacological appraisal, but by the workings of the machinery of bureaucracy. The outcome of the operation of these two sets of forces

may be release times which do not support the 'significant drug, fast track' hypothesis. This is what appears to have happened.

ATTRACTIVENESS OF MARKETS

The attractiveness of markets is likely to be a significant influence on the rate of inter country spread of drugs. Wealthy countries with large markets for pharmaceuticals, may exert a strong commercial pull and attract foreign developed drugs earlier than other poorer nations with less purchasing power. If this is true there should be a strong and negative correlation between the arrival time lag of new pharmaceuticals and the commercial attractiveness of destination countries. When absolute sales values of pharmaceuticals by country are used as market indicators, this correlation turns out to be very weak but does have the expected sign. Either absolute sales values are poor proxies for the attractiveness of markets, or something is operating to nullify the commercial pull of wealthy nations. Again anticipating the results, the influence nullifying the expected correlation may well be regulation. There would appear to be a strong relationship between the 'tightness' of countries' regulatory systems and the size of their market for pharmaceutical products. The large market nations appear to have the tightest regulatory systems, and the less wealthy nations appear to have much less tight regulatory regimes. In effect tight regulation may well modify the commercial attractiveness of wealthy markets by imposing lengthy and highly cautious pre-release appraisal on new drugs. The natural pull of sizeable markets may thus be neutralised by regulation. Poor nations may benefit by a diversion of interest towards them because of their less demanding drug clearance procedures. A weak correlation between absolute sales values and arrival time lags may thus result. This is what appears to have occurred.

COUNTRY TYPE

The type of country may well be relevant to the speed of acceptance of drugs. Developed nations are likely to be scientifically sophisticated and also have large markets for new pharmaceuticals. Less developed nations on the other hand are likely to be lacking in pharmacological expertise and have limited purchasing power for new drugs. It is therefore reasonable to suppose that there will be a marked contrast in

the diffusion times between the two general types of countries. However predicting what the difference might be is not simple. Two major influences that have already been mentioned above are likely to predominate. These are regulatory tightness and market size. As it turns out, the less developed nations are also those which are relatively loose in the regulatory sense. But the comparative ease of entry through their drug screening processes will not necessarily prompt the early arrival of new pharmaceuticals, because the markets for them are small. This seems to be true at least for the pre-1–71 portion of the sample. Developing countries tend to be late receivers of drugs. Later on the position seems to change and in the post-1–71 period the signs are that pharmaceuticals are tending to arrive earlier. Apparently companies are beginning to appreciate the value of these smaller markets, perhaps prompted by the stringent regulatory conditions being applied in the developed nations. So much has the relative position improved that there is no longer a statistically significant difference between the mean arrival time lags for the two groups of nations. It would now seem that small markets are more attractive because regulation has become so stringent in the wealthy nations of the world.

DETERMINANTS NOT STUDIED

The dotted line in Figure 1.1 indicates the factors that have been investigated in this study. Evidence has been collected on all of those that are above the dotted line. Those below the dotted line have been neglected. This is not intended as a comment on their importance, but reflects the difficulties involved in collecting information on them. It may well be that some of the most significant influences on the rate of spatial diffusion of drugs, is amongst those that have not been investigated. It is hoped that the major factors have been included in this study, but the possibility has to be admitted that this may not be so. In fact the low values for the multiple correlation coefficients (R) found here support the contention that the list of independent variables is deficient. However there is an alternative explanation, which turns on the way in which regulation effects the global spread of pharmaceuticals. This asserts that the impact of drug appraisal by regulatory authorities is such that high correlations are unlikely to be found. Official intervention in the process of spatial diffusion, may be such that the addition of extra variables will do little to improve explanatory power. The truth probably includes a mixture of both explanations. Regulation may well

work in the way indicated, and there may well be extra independent variables that could usefully be added. Some possible candidates for inclusion are discussed below.

THE TYPE OF FIRM

The type of firm is likely to be highly relevant to the rate at which new pharmaceuticals spread around the world. If a discovery takes place within a multinational company, it is reasonable to suppose that the global reach of such an organisation will facilitate spatial diffusion. A similar discovery within a small company that is merely national in scope, may be slow to spread. Inter country diffusion may be inhibited because of the localised nature of the company. No attempt has been made to collect data on the multinationality of companies. The difficulties in classification are great and the problems involved in handling such information are considerable. Previous experience served to warn the author to keep away from this area.[5] However it must be conceded that multinationality may well be a crucial element influencing the international spread of pharmaceuticals. The presence of subsidiaries in foreign countries probably ensures that knowledge of host regulatory systems is excellent, and that the means are available for fast distribution of drugs once clearance has been given. It may be that the decline observed here over the period 1954 to 1978 in the average time for drugs to spread between countries, is a direct result of pharmaceutical companies becoming more multinational. This is a genuine possibility and is admitted as such. There are of course other reasons that may explain the decline in arrival time lags. However in the absence of evidence on the impact of multinationality, these alternatives do not dispel the genuine concern that a major influence may have been neglected.

PATENTING CONDITIONS

Another factor that may be relevant to the rate of inter-country diffusion is patents and patenting conditions. The ability to defend proprietary knowledge is believed to be an important influence on the size of research effort in the Pharmaceutical industry.[6] Countries that do not permit patents for drugs, or who are not members of the Convention for the Protection of Industrial Property may be a problem.[7] Appendix 1

sets out some information on membership of the Convention and the types of protection available in the countries being studied here.

Types of protection vary widely between nations. How the timing of drug introductions is affected by patenting conditions is difficult to predict. Even in countries where there is no patent protection for drugs, it is not obvious that late arrival will be inevitable. Companies may feel impelled to deter rivalry and imitation, by early introduction. In effect they may attempt to defend their investment in locations where drugs are non patentable, via the good-will generated by early introduction and technological lead time. In like manner, it seems reasonable to suppose that non-Convention countries might suffer and thus be late receivers of new pharmaceuticals. On reflection however this is not so obvious. For non-Convention countries that have protection for drugs, an appropriate company strategy may be simultaneous patent applications. By applying on the same date in the non-member countries, the prior publication rule will not operate to disallow patents. As long as an application has also been made on the same date in one Convention member country, then the twelve months priority rule will apply. A year will thus be available to make applications in other member countries. On this strategy patent applications would tend on average to be earlier in non-member countries. Whether earlier introduction of drugs follows is of course another matter for reasons outlined below.

There need be no close relationship between the timing of patent applications and the dates of regulatory clearance. The starting point of patent terms is likely to be relevant here. Some countries define the beginning from the date of grant, others from the initial application, and yet others from the filing of complete specifications. Presumably patent applications can afford to be earlier relative to clearance, where the term is based on the granting date. Processing time for search and validation which is usually between two and three years, will not shorten the effective life because this starts only after granting. Companies will attempt to mesh regulatory clearance and patent grant times to avoid the situation where a patent is granted but the drug may not be publically distributed. If this occurs effective patent life will be shortened because sales may not take place. The commercial life of the patent is thus reduced. Pressure to avoid such a timing mismatch is however likely to be much greater in systems where the start point is based on the time of patent application. With these, processing time reduces the life of patents. There is therefore likely to be much greater concern to avoid a situation where regulatory clearance occurs after patents are granted. If this happens there is yet another erosion of effective patent life, which is

in addition to that already incurred by the search and validation process. Thus where patents are likely to be truncated in this way, companies will presumably tend to apply late relative to submissions for regulatory clearance.

The analysis of the relationship between the date of patent application and regulatory clearance is of course greatly oversimplified. It has been presented as if a major concern of the innovating companies is to ensure that there is no time mismatch. In practice technological rivalry and hence the 'race to the patent office' may be so frantic that an absolute priority is given to achieving early application. Registration of a claim to a patent may thus follow in 'pell-mell' fashion. Furthermore the device of including one Convention country amongst the simultaneous applications to non-Convention countries, obviously constrains the choice of timing of patent applications in particular countries. In non-member countries application has to be on the same date, and even in member countries the maximum time spread is only twelve months. Thus in practice the alignment of patent acquisition and regulatory clearance is likely to be pretty crude. The speed of operation of countries regulatory systems varies considerably. Any attempt to mesh patent granting with clearance is therefore likely to be fairly haphazard.

Returning to the general point that patents and patenting are likely to have an influence on the timing of drug introductions, this is accepted. *A priori* reasoning however gives little guidance on what the effects are likely to be. The complications of Convention and non-Convention systems prevent any simplistic prediction. In addition the problems are compounded by the type of company involved. It is probably the case that large companies which are multinational in character, are likely to be particularly effective in their use of the application devices described above. They will be big enough to have a large patents department and will be familiar with a large number of countries' patent systems. This familiarity is likely to be an almost automatic by-product of a direct physical manufacturing presence in foreign locations. Multinationalism and an effective use of patents world-wide are thus likely to go hand in hand. The lack of evidence on multinationalism and patenting conditions in destination countries, is a serious deficiency. The author attempted a type of classification system for patents but gave up under the weight of the complications. The most difficult element was to appraise the 'quality' of countries' patent law. Quality is a nebulous concept and is made up of such elements as respect for the law, consistency in operation, and the predictability of legal judgements. However the practical difficulties of appraisal were such that early in the