REGULATORY AUTHORISATION OF CLINICAL TRIALS

The problem

During the 1970s, research-based pharmaceutical companies became increasingly frustrated and impatient at the delay in obtaining authorisation for conducting clinical trials with new compounds in the UK compared with nearly all other countries. This delay had two origins. The first was the requirement for laboratory data which was virtually as detailed and extensive as that required elsewhere only at the marketing (product licence) stage. The other was the 6–12 months delay in processing applications through the government system. The effects were serious in encouraging companies to divert early clinical testing overseas and in depriving clinical pharmacology departments in the UK of an opportunity to take part in clinical development. The Association of the British Pharmaceutical Industry (ABPI) set up a working party to tackle the first problem by studying the data requirements to see if they could be modified so as to allow clinical trials to be safely conducted on the basis of different data. It concluded that this could be done by a phased approach in which the numbers of patients and the duration of their exposure to drugs was limited initially depending on the results of early laboratory testing. Extension of the clinical work would then be possible as the laboratory safety data was extended. This would have several advantages including the acceleration of development. The numbers of animals used would be reduced as well as the costs and would allow a larger number of candidate experimental compounds to be tested in patients. Laboratory research often offers several similar compounds and the need for full development before clinical trials meant that previously only one could be selected. Hence, limited clinical testing of several compounds could improve the chances of selecting the best one for eventual marketing.

The Committee on Safety of Medicines (CSM) also set up a Working Party under the chairmanship of Professor Grahame-Smith to study the same subject. Happily the Grahame-Smith group largely accepted the ABPI proposals and their recommendations were published in January 1981 (MLX 130). The new data requirements were formally announced in the Medicines Act Information Letter No. 32 in November 1981.

The exemption scheme

Along with this change in data requirements the licensing authority explored ways of reducing the

processing time of applications and a decision was made to utilise a provision in the Medicines Act (1968) which allowed, under certain conditions, for an exemption from the need to hold a Clinical Trial Certificate. This system is described in the paper by Speirs & Griffin (1983). It was strongly welcomed in principle by industry, although reservations remained about how efficiently it would work in practice; many previous attempts to improve procedural delays had been disappointing. The new time scales envisaged were very ambitious and the system relied heavily on the secretariat of the Medicines Division of the DHSS who would take responsibility for granting the exemptions without reference to the CSM. The 'licensing authority' as empowered in the Medicines Act (1968) can seem a rather intangible body; it is ultimately the Minister of Health although for most practical purposes delegated to officers of the DHSS. The CSM and other part-time Section 4 (of the Act) Committees are advisory to the licensing authority. The new scheme meant that the licensing authority would be acting on its own, and the responsibility of the company would be increased. One concern was the way hospital ethics committees would view the new system. The DHSS took measures to reassure these committees that they would not have to assume any new responsibilities for the safety of the compound under test and this seems to have been successful. New delays have not arisen at ethics committee reviews. Other fears were about delays due to repeated applications that might be needed during the expansion of clinical trials and the frequency with which the 28 day extension would be needed. Neither of these features have been a problem although the data given by Speirs & Griffin (1983) do not bear on this. An ABPI survey of its member companies does however give data on this aspect and is perhaps worth giving in full (Table 1). The questionnaire covers the period 1 July to 31 December 1982 and is thus 1 year later than the Speirs & Griffin (1983) data.

Table 1 Questionnaire to ABPI members

Number of companies responding to questionnaire	53
Number of companies who had made CTX applications	41
Number of CTX applications	93
Number of new chemical entities	35
Applications receiving clearance within 35 days	78
Application receiving clearance within 35 + 28 days	7
Applications not accepted	8

We cannot assume that these figures as returned include all the applications made in that time but they are close to those of the earlier year of about 100 in 6 months. Only seven applications of the 85 approved were delayed into the 28 day extension. Of the eight applications rejected four are now being presented as an application for a Clinical Trial Certificate, two were subsequently accepted and the fate of the other two is unknown. The number of new chemical entities of 35 in 6 months is also comparable to the Speirs & Griffin (1983) survey. The ABPI survey also revealed that variations to the exemptions given were promptly dealt with and that Ethics Committees had not created delays.

It is as yet too early to resolve one remaining concern. This relates to the absence of any examination by the CSM of data on the product until it is presented with an application for a product licence. One advantage with the old system was that once a Clinical Trial Certificate had been obtained a company could be fairly reassured that its safety testing laboratory data was satisfactory. Under the new scheme it is theoretically possible for the CSM to demand extra laboratory work at this late stage and introduce a new delay. However, guidelines on the full data expected for product licence applications and informal discussions between the company and the licensing authority beforehand should make this an unusual occurrence.

Response to the scheme

The new system has made new demands on both the licensing authority and on companies but it is probably fair to say that these have generated not only a more efficient system, but a better integration of the two roles. This, in part, could also explain an improvement in relationships between the two parties, that has taken place in the same time. The company is compelled to summarise its data to give a meaningful picture of the compound's properties as a whole and a company medical adviser has to certify that the proposed clinical work is reasonable in view of these properties. The licensing authority accept this summary as giving a true reflection of the detailed data (which is not seen). It is then the subject of 'negative vetting' such that if the company demonstrates the adequacy of the data as a basis for a clinical trial then no objections are made.

The Speirs & Griffin (1983) data and the ABPI data speak for themselves in terms of speed of processing and number of applications. But it is not certain if the number of new chemical entities undergoing clinical evaluation in the UK has increased as a result of the scheme. As Speirs & Griffin (1983) state the number of Clinical Trial Certificates was falling in the preceding years and the average number of new chemical entities was less than 40 per annum. During this time

the number of trials being conducted under the responsibility of doctors (rather than companies) was rising rapidly and may have included many new chemical entities. Further information on this topic is contained in an appendix added in proof to the article by Speirs & Griffin (1983).

The adverse reaction data also testifies as to the safety of both the new procedural scheme and the new data requirements—especially in view of the number of reactions that can be accounted for by only one, anti-cancer, compound. There is variability in both the collection of adverse reaction data and its delivery to the licensing authority due to very imperfect definitions in this area. Much is left to the discretion of clinicians and to company doctors as what is an adverse reaction, or what is an event, or what is major or minor. This is probably a subject that could be further investigated to clarify, and to make more uniform, the definitions. Along with this there should be a more standard interrogation and classification of reactions into their likely degree of causal relationship with the drug. However there is clearly nothing in the Speirs & Griffin (1983) results to suggest a problem with regard to clinical trials under these new conditions. These authors are disturbed by the delay in some applications between the granting of exemptions and the start of clinical trials. To those who have had to suffer the numerous vagaries involved in clinical trials and in being dependent on resources outside the company this will not be so surprising. However it should be looked at to be sure that other, unnecessary delays are not now revealed in clinical research.

How much the new system has speeded up company development time is difficult to say. So much depends on the way the total development programme has been planned, and for what type of products and for what regions of the world. Industry is very international in context. However the majority of UK companies have undoubtedly withdrawn much, but not all, of their early clinical work to this country to the advantage of clinical pharmacology and medicine generally. It is gratifying to see the high proportion of new chemical entities coming from UK research—16 of the 76 (nearly 20%) being tested here. This is particularly high in view of the proportion of world pharmaceutical research and development that is based in the UK, which is 10%. This in turn is high compared with the total UK market for medicines which is only about 4% of the world total. Incidentally this industry also provides employment for over 70,000 people directly (and more indirectly) and a surplus in the national balance of payments of £600m in 1982. These figures confirm both the confidence placed by industry in the UK as a place to carry out research and the skill of the British scientists in their fruitful efforts. Let us hope that this success will continue in spite of numerous general constraints

placed on the industry and will be supported by an optimal system for regulatory authorisation of clinical research.

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Reference

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