A SURVEY OF THE FIRST YEAR OF OPERATION OF THE NEW PROCEDURE AFFECTING THE CONDUCT OF CLINICAL TRIALS IN THE UNITED KINGDOM

C.J. SPEIRS & J.P. GRIFFIN

Medicines Division, Department of Health and Social Security, 1 Nine Elms Lane, London SW8 5NQ

Introduction

The scheme whereby pharmaceutical companies could seek exemption from the need to hold Clinical Trial Certificates was introduced in March 1981. This is referred to as the Clinical Trial Exemption Scheme or CTX scheme. The details of its operation have been previously described by Griffin & Long (1981) who also outlined five objectives of the scheme, which are that it may bring 'benefits to patients from newly marketed drugs having been adequately tested in the therapeutic environment of the United Kingdom, . . . that it enables industry to speed up the 'brain-to-bottle time'; it encourages the development of departments of clinical pharmacology both from the stimulus of new work and the financial support afforded by the industry; it provides an incentive for the research and development element of the industry to develop in the United Kingdom, and it eases the task of the Licensing Authority and the Committee on Safety of Medicines in assessing drugs at marketing stage if trials to a high standard have been conducted in the United Kingdom'.

Under the Clinical Trial Exemption Scheme the applicant is required to generate the same basic data to support the proposed clinical programme as it would to support a Clinical Trial Certificate application. (This is described in notes for guidance published, and periodically revised, by the Licensing Authority).

In the Clinical Trial Exemption Scheme, however, the applicant is required to send to the Licensing Authority only a certified summary of the data and not the data itself as would be required for a Clinical Trial Certificate application. A copy of the protocol(s) must also be sent together with confirmation by a doctor working in the United Kingdom as a medical adviser or consultant to the company that he has satisfied himself, in the light of the information submitted, that it is reasonable for the trial to take place.

The Licensing Authority has 35 days in which to consider the notification and summarised data and advise the company whether or not it objects to the proposed trials, or whether it requires a 28 day extension period in which the applicant may provide additional data or give assurances. (In practice this period

is often used by the applicant in a manner which renders the proposals acceptable to the Licensing Authority).

The grant of an exemption from the need to hold a clinical trial certificate imposes upon the holder of such an exemption the obligation to notify the Licensing Authority under four circumstances: (i) any change made to the protocol, (ii) adverse reactions arising during the trial, (iii) any other information casting doubt on the safety of the substance and (iv) any objections raised by an Ethics Committee to the proposed studies.

A brief survey of the Clinical Trial Certificate Exemption scheme was made earlier by Griffin & Stewart (1981) which examined the operation of the first 6 months of the scheme. All exemptions were included in the survey including biological products, and each strength of the formulation of the product was regarded as a separate exemption.

This study is presented as an interim report on the safety of operation of the Clinical Trial Exemption Scheme. It also catalogues the users of the scheme and the extent of its use but a full analysis as to how far the scheme has succeeded in its five previously quoted aims is beyond the scope of this paper.

Every effort has been made to detail all adverse reactions to determine whether or not any unacceptable hazard occurred in the clinical studies conducted under the scheme. To this end all reports of suspected adverse reactions are included in this paper. Because so many were extremely unlikely to have been caused by the drug they are referred to as *adverse events*. (This is NOT meant to indicate in any way that this paper is written on event-monitoring. Companies holding CTXs were simply asked for adverse reactions. However the replies received clearly included a large number of non-drug related events. These may have been included for a number of reasons. For medico-legal reasons the companies often include even the most doubtfully drug-related events particularly if serious, and this seemed to particularly include deaths. The rule for queries was if in doubt report as the aim was to be as inclusive of any possible adverse reaction

data as possible). Also in an attempt to achieve completeness the designation 'major' to describe adverse events was deliberately made as wide as possible (see below) and includes many non-serious side-effects, for example because they led to a patient dropping out of a study. The terms adverse event and major adverse event are therefore used rather idiosyncratically throughout because of the diverse nature of the data base (company responses to questionnaires) and the need here for full reporting.

Methods

A computer print out was obtained for all applications made during the first 12 months of the operation of the Clinical Trials Exemption Scheme. A letter was sent to all pharmaceutical companies which had been granted exemptions requesting completion of a simple questionnaire. For each drug formulation under trial a separate form was provided to allow documentation of the following points:

- Number of patients recruited to trial programme
- The numbers of adverse reactions
- The nature of the adverse reactions
- The outcome to the patient.

It became clear, however, that many companies were reluctant to differentiate between adverse events related to the drug and those related to other factors, such as the disease under treatment. This may have been because of the medical time required to achieve any satisfactory division and also because of medico-legal implications. Thus the information submitted in response to the questionnaire was largely unsorted data reported from the investigating doctors to the company and passed on to the Licensing Authority. All these reports are referred to subsequently as adverse events. The companies were also asked to state whether they regarded the adverse events as being major, for example when patients were withdrawn from trial due to the side-effects or when the coding of a double blind trial had to be broken, or minor. Any adverse comments or refusals from Ethics Committees were also to be entered along with any other particular comments.

The first questionnaire was posted in April 1982. The initial letter was followed by a reminder letter 3 weeks later and this was followed by telephone calls to slow responders. The cooperation achieved was good, i.e. 100% return of questionnaires by the end of July 1982.

In order to obtain conformity and as outlined in the introduction, in order to highlight all possible serious drug reactions a re-categorisation of the reported adverse events into major and minor was made after return of the questionnaires. An adverse event was called 'major' if it satisfied any of the following criteria:

- (1) it was classified as such by the clinical trial investigators or by the responsible company;
- (2) it resulted in a patient dropping out of the trial;
- (3) it resulted in the breaking of a double-blind code; or
- (4) it involved an important physiological disturbance e.g. any unexplained depression of blood count, any blood dyscrasia, jaundice etc.

This operation was repeated at a further follow-up in October 1982, 6 months after the first questionnaire had been circulated. The same cohort of exemptions—that is all those granted in the first year of operation of the scheme—was followed up in the same way. In addition on this occasion the companies were asked to supply the country of origin of any new chemical entities being investigated under the scheme. A similarly high return of questionnaires was attained on this occasion. (The only omission was a failure to identify the country of origin of a new chemical entity).

Results

Applications for Clinical Trial Exemptions (CTX)

A total of 210 applications for CTXs for synthetic chemical products or combinations of such products was received by the Licensing Authority during the period 1st April 1981–31st March 1982 (Table 1), different strengths of a formulation were regarded as a single exemption as this method of accounting was considered more realistic than that used earlier by Griffin & Stewart (1981). Two hundred and three applications for a CTX were granted on the initial presentation of the summary data, four applications for clinical trial exemptions were inadequately presented initially but on re-presentation were granted exemptions. A total of 207 clinical trial exemptions were therefore granted in the period of the survey and were the subject of further analysis.

Two applications for exemptions from the need to hold CTXs for biological products such as vaccines, blood products, etc. were excluded from this survey.

Applications for Clinical Trial Exemptions refused

In three applications (involving new chemical entities) the summaries contained material that indicated that toxicological problems existed which could not be properly evaluated from summary data, and that a full assessment of the original data would be necessary before the product could be adequately assessed. One of these applications for exemption has subsequently been represented as an application for a clinical trial certificate with the full data. Limited clinical exposure of patients to this substance has been approved by the Licensing Authority after the advice of the Committee on Safety of Medicines had been received.

Table 1 Progress in clinical trials under CTX scheme and adverse reaction reports

Total number of clinical trial exemption applications	210
Total number of clinical trial certificate exemptions granted	207
Number in which studies have not started	36
Number in which no reactions have been noted	80
Number in which reactions have been reported	87
Terminated CTXs	4

Clinical Trial Exemptions suspended

Four clinical trial exemptions were suspended on grounds of safety, two because adverse toxicological effects had been identified by the company in long-term animal safety studies and in neither case had patients been exposed to the drug. One clinical trial exemption was suspended because of biochemical changes detected during the trials, but no patient experienced any subjective adverse reactions. The fourth drug was withdrawn from trial after adverse changes in haematological monitoring had been detected; again no patient experienced any subjective adverse effect, only changes in laboratory measurements. In the two evaluation programmes where the studies were terminated the total number of patients exposed to the drug substances in the UK was less than 30 patients.

Ethical Committee problems

Problems related to the ethical considerations in trials conducted under the clinical trial exemption scheme were few. Only two programmes experienced serious objections raised by ethical committees. One of these related to failure to reach agreement on compensation under product liability for potential injury that might have arisen during the studies proposed. The other was a more serious ethical objection to the conduct of the trial.

New chemical entities (NCEs)

In the 207 trial certificate exemptions granted there were 76 exemptions for drug substances not marketed in the United Kingdom (Table 2). (However, six of these substances had previously obtained a clinical trial certificate). These 76 drug substances were classified as new chemical entities.

Three applications to conduct clinical trials on new chemical entities under the clinical trial certificate exemption scheme were refused during the period of the survey. The total number of applications for evaluation of new chemical entities under the clinical trial exemption scheme was therefore for 79 drug substances.

Table 2 Clinical trial exemptions applications relating to new chemical entities

Applications for CTX for new chemical entities	79
Applications for CTX for new chemical entities approved	76
Applications for CTX for new chemical entities refused	3
Trials on new chemical entities not commenced within 6 months of CTX approval	12
Trials on new chemical entities discontinued due to suspension of CTX on grounds of safety	4
New chemical entities under current evaluation	60

Origin of new chemical entities

In Table 3 the country of origin of the companies applying for clinical trial exemptions is indicated. British owned companies applied for and obtained clinical trial certificate exemptions for 38 products which included 11 new chemical entities. In Table 4 is shown the country of origin of 75 of the 76 new chemical entities originated in the United Kingdom exemption scheme, and it is seen that 16 of the new chemical entities originated with the United Kingdom.

The largest number of new chemical entities being evaluated originated from the United States 23, with Switzerland 9, West Germany 7 and Japan 5, making a considerable contribution.

One United States owned company with a United Kingdom research base presented 17 applications for new chemical entities, and one British owned company obtained exemptions to evaluate 7 new chemical entities. However most new chemical entities were being evaluated by companies which only had one or two new chemical entities under clinical trial.

Delays in starting clinical studies after grant of clinical trial exemption

In the first year of operation of the clinical trial exemption scheme from 1 April 1981–31 March 1982, 207 exemptions from the need to hold a clinical trial certificate were granted. At the completion of the second questionnaire recording the situation at 30 September, 1982, the clinical evaluation of 36 products had not commenced. All these exemptions had been granted at least 6 months. Fourteen clinical trial exemptions had been granted 12 months or more previously, but the clinical trial programme still had not been initiated. Of the 36 products whose clinical evaluation programme had not commenced 12 were new chemical entities.

Five of these 36 products whose clinical evaluation programmes have not commenced, have been temporarily shelved for commercial reasons unrelated to the safety of the product. The reason for the 6 month or greater delay in evaluation of the other 31 products (including 12 new chemical entities) is unknown.

Table 3 Total CTX applications by companies in the first year of the scheme

	Total	New chemical entities*
British owned	38	11
Foreign owned with U.K. research base	81	28
U.S. owned	25	2
EEC owned	40	21
European non-EEC	21	6
Other	5	2
Total	210	70

*New chemical entities to the U.K. licensing system—excluding those with pre-existing clinical trial certificates (6), and three which were not granted.

Table 4 New chemical entities under clinical evaluation under exemptions by country of origin

<i>Country of origin of new chemical entities being evaluated under the CTX scheme in the United Kingdom</i>	
United States	23
United Kingdom	16
Switzerland	9
West Germany	7
Japan	5
France	4
Italy	4
Belgium	3
Holland	1
Sweden	1
Norway	1
Czechoslovakia	1
Not disclosed	1
Total	76

Time in processing applications for clinical trial exemption

All the applications for exemptions from the need to hold clinical trial certificates have been handled by the Licensing Authority in the first year of the scheme within the time limits laid down. The average time to process an application for a clinical trial certificate in 1979–1981 varied from 4–8 months. The exemption scheme therefore has speeded up the process of introducing new products into clinical evaluation, as far as regulatory delays are concerned.

Adverse events during clinical evaluation programmes

Up to the end of November 1982 a total of 11,351 patients had been entered into studies under exemptions granted during the first year of the scheme's operation; 4,244 were patients participating in studies involving new chemical entities and 7,107 in studies of

licensed drugs. Some of these patients would have been taking placebo or comparator drugs. Similarly at this juncture it was not always possible to distinguish between minor side-effects associated with the study drug and those associated with comparator or even placebo in many of these studies as they were 'blinded' and the codes remain unbroken in the great majority at this stage. Indeed of the 87 clinical trial programmes where adverse events were reported only 10 were complete and of these only three are written-up so far. Eighty programmes have had no adverse event reported to date, many of these are double-blind studies in which only serious events requiring the code to be broken could be expected to have been reported.

The total incidence of all adverse events both major and minor to November 1982 was 840 in a total of 11,351 patients (7.4%). It should be noted that 4,975 patients were in studies (mainly of well known drugs) where no events have been reported *so far*. This has undoubtedly given a falsely low incidence of adverse events with established drug substances and combinations, compared with that seen with the new chemical entities. However the major side-effects should be equally revealed in all studies as can be seen from Table 5; 81 major adverse events were reported from studies involving known and marketed drugs in 7,107 patients (1.14%) whereas with studies involving new chemical entities there were 70 adverse events in 4,244 patients (1.65%).

Deaths reported in the studies

A total of 26 deaths in 11,351 patients are reported, none of which was thought to be caused by the drug under investigation in the judgement of either the responsible physician or the company monitoring the study. Twenty-four of the deaths occurred in a single evaluation programme involving over 800 patients with severe infections being treated with a cephalosporin antibiotic. The two remaining deaths were in chronically ill patients with terminal respiratory and cardiac disease. In the studies concerned a high in-

Table 5 All events in clinical trials conducted under the CTX scheme for known active ingredients and for new chemical entities presented separately

	Number of products being evaluated under CTX	Total patient numbers enrolled	Adverse events Actual numbers (%)	
			Major	Minor
CTXs involving known active ingredients already on the UK market	107	7,107	81 (1.14%)	319 (4.48%)
CTXs involving new chemical entities	60	4,244	70 (1.65%)	370 (8.72%)
Totals		11,351	151	689

cidence of disease-related mortality was expected and the investigational drugs were not suspect in either direct toxicity or lack of efficacy. All these reported deaths were ascribed by the responsible clinician to the disease (or diseases) being treated.

Analysis of major adverse events

For the purposes of this paper 'major' events were taken to include any, even relatively minor events, which resulted in patients being withdrawn from the study. The data was *clearly inadequate for an assessment of drug culpability* although it is noted that in a considerable number of cases, causal relationships to the investigational drug was unlikely. As can be seen from Table 6 the reasons for withdrawal with new chemical entities tends to be rather different from those with the established drugs. The new chemical entities had a higher incidence of reported laboratory abnormalities, without associated clinical findings. The 'severe' group of adverse events include hallucination, a recurrent and perforated peptic ulcer,

drug sensitivity, dyspnoea, cardiac failure and myocardial infarction, syncope, colitis, hypertension and a Herxheimer reaction in a patient with previously undiagnosed syphilis. Four cases of bleeding occurred with a fibrinolytic agent. The abnormalities of clinical signs and laboratory parameters in the absence of any symptoms were heavily weighted by 19 reports from a single agent—a new chemical entity used in the treatment of malignant disease.

Discussion

The total number of applications for Clinical Trial Exemptions in the first 12 months of the scheme's operation covered 210 drug substances or combinations of drug substances (different strengths of formulations of the same product were regarded as a single exemption and biological products, i.e. vaccines, blood products, etc were excluded). A total of 79 new chemical entities were included in this number. In the preceding 8 years the number of clinical trial certi-

Table 6 Reported 'major' adverse events

	Number of adverse events in patients in trials of new chemical entities	Number of adverse events in patients in trials of marketed drugs
Total numbers of patients exposed	4,244	7,107
Patients with minor symptoms (nausea, headache, dizziness, uncomplicated skin rashes etc.) reported as major because patients were withdrawn from study	8	61
Patients with severe symptoms without abnormal laboratory findings	15	12
Patients with laboratory abnormalities in the absence of symptoms	25	1
Patients with both symptomatic and laboratory abnormality	1	1

N.B. Excluded from this table are 26 unrelated deaths; also one further 'major' adverse event associated with placebo.

ificates issued in the United Kingdom had fallen from 170 in 1972 to 87 in 1980 (Griffin & Diggle, 1981) with an average of less than 40 new chemical entities being evaluated in the 3 years 1979–1981. The exemption scheme has therefore resulted in its first year of operation in a threefold increase in the number of studies being conducted and a nearly twofold increase in the number of new chemical entities being evaluated. The opportunity for clinical research has been grasped mainly by U.K. companies and international companies with a research base in the U.K. It is interesting to note that the original source of new molecules is often different from the country of origin of the company evaluating the new chemical entity.

A disturbing feature is the delay which has occurred in the commencement of a number of studies. Clinical evaluation of 36 products had not commenced 6 months after grant of the exemption including twelve involving new chemical entities. Fourteen products had not commenced their clinical evaluation programme one year or more after the exemptions were granted.

Four products have had their exemption from the need to hold clinical trial certificates cancelled which represents less than 2% of the exemptions granted.

This survey presents adverse reaction data from a wide variety of clinical trials which are mostly still on-going. The main reason for it being carried out was to assess the progress of the Clinical Trial Exemption scheme especially in regard to safety. The overall incidence of reports received includes a substantial number associated with comparator products or placebo. A large number of the others reported here were clearly not drug related, but the data was inadequate for a true culpability assessment. It is neither possible nor relevant to obtain a true 'incidence of side-effects', but the comprehensive replies received together with the statutory legal requirement of reporting of serious adverse reactions do, it is believed, permit a confident assessment of the maximum incidence of serious adverse effects in this cohort of patients.

Those patients most at risk might have been considered to be those who were taking those drugs whose investigations were terminated on grounds of safety. In fact, of the four products in this category two were not administered to patients because the programmes of clinical evaluation were cancelled on the basis of results from chronic animal toxicology studies prior to patient exposure. The two other exemptions were terminated following abnormal haematological and biochemical laboratory findings; no patients in these studies experienced serious symptoms nor any long term consequences of taking the drugs. The other 'major' side-effects with new chemical entities were all defined as major because they resulted in patients being withdrawn from the

studies. There were no deaths attributable to the drugs. A total of twenty six deaths occurred in the studies but were clearly ascribed by the investigating physicians to the underlying disease being treated rather than to the drug substance. No life-threatening results of drug exposure were reported nor were any permanent ill-effects apparent.

When considering this profile of adverse events it has to be remembered that with drugs used in the treatment of particularly serious diseases a high incidence of serious side-effects may be tolerable. In this context of the adverse events shown on Table 6 nineteen out of 25 major laboratory abnormalities were associated with one particular new chemical entity used in patients with neoplastic disease. This drug has subsequently been approved for marketing following advice from the Committee on Safety of Medicines. Also a number of deaths occurred where more detail was provided demonstrating that the drug association was most unlikely to have been causal. The incidence of adverse events given in Table 5 of 1.65% for new chemical entities and 1.14% for marketed drugs is not corrected for these factors and the difference in rates may also be influenced by other factors. For example it is likely that the monitoring required by the clinical trial protocol affected the incidence of reports. Laboratory monitoring is naturally more extensive and frequent with new drugs and can be expected to reveal more abnormalities both related and unrelated to this category of drug. Reporting of adverse events included such episodes as a Herxheimer reaction caused by the treatment of a case of gonorrhoea with concomitant syphilis—an event caused by the problem of clinical practice, not by drug toxicity. Indeed it is suggested that the frequency and thoroughness of safety monitoring is as important in the safety of administration of these investigational drugs as is their own intrinsic toxicity.

Conclusion

The first year of operation of the scheme providing the option for pharmaceutical company to apply for an exemption from the need to hold a clinical trial certificate supported by verified summary data as opposed to making a detailed submission for a clinical trial certificate has indicated that the Licensing Authority has been able to process all applications received within the time limits allotted. The results of this survey indicate that the number of new chemical entities submitted for clinical evaluation has increased two-fold in the first year of operation of the scheme compared with the average of the previous 3 years. The scheme has operated at no increased hazard to the patients participating in the clinical studies.

References

- GRIFFIN, J.P. & DIGGLE, G.E. (1981). A Survey of products licensed in the United Kingdom from 1971–1981. *Br. J. clin. Pharmac.*, **12**, 453–463.
- GRIFFIN, J.P. & LONG, J.R. (1981). New procedures affecting the conduct of clinical trials in the United Kingdom. *Br. med. J.*, **283**, 477–479.
- GRIFFIN, J.P. & STEWART, A.G. (1981). Six months experience of new procedures affecting the conduct of clinical trials in the United Kingdom. *Br. J. clin. Pharmac.*, **13**, 253–255.

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Appendix

The effect the new procedures have had on the rate of applications from doctors and dentists requesting exemption from the need to hold a clinical trial certificate, as allowed by 'The Medicines (Exemption from Licences) (Special Cases and Miscellaneous Provisions) Order 1972 SI1972 No 1200 has also been monitored.

No record of how many of these applications represented the first use of a new chemical entity in patients is available. New chemical entities were, however, first used in patients in the United Kingdom under these exemption procedures, particularly in the area of cancer chemotherapy.

Table 1 Applications from doctors and dentists from exemption from the need to hold a clinical trial certificate 1972–1982

<i>Year</i>	<i>CTC exemption applications from doctors and dentists</i>
1972	49
1973	203
1974	201
1975	200
1976	184
1977	241
1978	284
1979	356
1980	320
1981	265
1982	245

In 1981 and 1982 there has been a lower annual rate of applications than that seen in the years 1979 and 1980.