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SOME PROBLEMS IN THE U.K. WITH THE PROVISION OF NEW DRUG DOSAGE FORMS FOR PRE-MARKETING TESTS IN MAN

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Provision of dosage forms for studies in man calls for the highest standards of Good Manufacturing Practice. Problems with supply of such materials are classed as scientific/technological, logistic, ethical and legal, and examples are discussed. The role of the formulation pharmacist as an influence on harmonizing the nature of dosage forms used in multi-centre trials on an international basis, and as a person involved in ensuring smooth transition of products from clinical trial status to production for marketing purposes is highlighted.

It will be noted from the title that use of the term "clinical trial" has been avoided and this has

been done in order to widen the scope of the discussion to include consideration of the problems faced by the industrial pharmacist in supplying materials for human volunteer studies. Many of the problems are common to both stages of drug development, but there are additional features associated with volunteer studies which make it worthwhile giving special consideration to those materials intended for the first studies in healthy human beings. The problems at all stages can be classified under four main headings (Figure 1).

It is proposed to concentrate on the first two headings, although of course the pharmacist cannot remain aloof from the ethical aspects of drug supply and certainly there are legal controls relating to

1. SCIENTIFIC/TECHNOLOGICAL
2. LOGISTIC
3. ETHICAL
4. LEGAL/REGULATORY

FIGURE 1

Classes of Problem

provision of materials consumed by human beings, to which reference will be made.

As a preliminary it can be said that the extent of the problems of the four types given in the first Figure will differ somewhat according to the disease indication for the drug, the route of administration, the dose and of course the physico-chemical nature of the drug. This paper will deal in a general way with difficulties encountered with the more traditional dosage forms, but the problems to be expected with less common products such as powder inhalations, aerosols and perhaps suture materials would require special consideration.

Since the materials we are talking about are for administration to man, we have a pharmaceutical responsibility to provide materials to the same standards of identity, quality, purity and safety as are required for marketed products. In practical terms the highest standards are required; the criterion being one of potential self administration. The full achievement of this ideal, particularly at the earlier stages of a programme may well be thwarted to a degree by lack of drug substance, lack of defined discriminating assays and so on. Implicit in this concept is a need for

independent responsibility for quality control of such dosage forms and this may vary between companies. In essence, all the tenets of GMP should apply to experimental dosage forms intended for human administration and of these tenets, the importance of competent staff, careful referenced documentation, avoidance of cross contamination between products and of course good dispensing practice should all be emphasised.

Let us turn now to materials used in human volunteer studies. In UK and some other countries, drug regulatory authorities do not lay down restrictions on the administration of new drugs to healthy volunteers : control is exercised only in clinical trials and on the marketing of products. The volunteer study represents the first administration of the drug to man and follows upon completion of, and to quote from the ABPI Guidelines published in September 1977, "adequate pharmacodynamic, pharmacokinetic, reproductive and toxicological studies to justify progression to human studies". These Guidelines indicate that the formulation should be the simplest presentation consistent with the objectives of the study and should be consistent with the formulations used in the preliminary screening and animal toxicity tests. It has been recorded that in some instances toxicity testing

was carried out using solid unmilled drug substance followed by human bioavailability tests with micronized drug. Pharmacists can contribute to the vigilance necessary to avoid the potentially grave consequences of errors such as this.

Now the purpose of the volunteer study may be to provide information on several aspects of drug action including tolerance, dose ranging, pharmacokinetic and pharmacodynamic data, and to seek to identify any early incidence of drug toxicity. At this stage, suitable assay methods for drugs and metabolites in biological fluids may not be available and to avoid delays radioactively labelled drug may be used. In this situation, logistic problems are immediately apparent and they lead in turn to technical problems with the production of small quantities of dosage forms with possibly atypical properties. Again it is worthwhile stressing that care and attention to detail are essential to safety and to ensure that such factors are taken into account in the interpretation of the results obtained.

We have found that it is not uncommon to have requests for parenteral forms for early volunteer studies. For instance, there may be a short list of

two or three analogues of a lead compound and all that is required is to learn which of the materials has the desired excretory pattern. We are faced usually with inadequate drug supplies for thorough formulation studies. The formulation requirement is to investigate drug solubility and stability with a view to producing an injectable solution which has adequate stability for the test period and which is not unacceptably painful on injection. This should, if feasible, have undergone a terminal heat sterilization process. The development of valid stability data which depends on the availability of a reliable, reproducible, stability-indicating assay method is a key requirement in this context. The availability of appropriate and timely analytical support is vital.

Ethical considerations too bear heavily on the pharmacist's responsibilities : responsibility to the clinician conducting the study and to the participating volunteer subjects. The volunteer will normally be operating on a basis of informed consent and can expect to have assurance that the product to be administered is made correctly and to an appropriate and defined specification.

From a legal point of view, volunteer studies are not controlled in UK by the Medicines Act. However, the

application of Common Law has allowed companies to vary in their interpretation of the onus of responsibility. Generally speaking, the responsibility will be seen to rest with the clinician authorising administration of the drug to the volunteer and this will be implicit or in some cases explicit in Company regulations governing the performance of such tests. However, there can be no doubt that there could be considerable repercussions if negligence on the part of the pharmacist preparing the dosage forms was shown to be a factor contributing to untoward effects seen in the study.

Turning now to supply of materials for clinical trial, the essential difference is that here the supply is subject to the provisions of the Clinical Trial Certificate (CTC). This is granted on the basis of data, including formulation details, included in the CTC Application. However, it is important to mention the special situation where materials are supplied on a so-called "Personal Investigational New Drug" basis. Here the physician is carrying out a very early study on a new drug or a drug for a new indication in a few selected patients, on his own responsibility. In this circumstance, approval is given by the Regulatory Authority for the limited supply of material for this specific purpose, the physician having obtained agreement of his local Ethical Committee. The difficulty

here may be that there has been insufficient time for full formulation development to be carried out and in particular a short shelf life may have to be stipulated and special storage conditions detailed.

Provision of supplies for clinical trial present pharmaceutical companies with a dilemma : should substantial quantities of drug be made available and time allocated to ensure that the dosage forms used in trials are fully optimized and which, provided the trial results are favourable, are identical with the marketed product? Generally speaking, although different company attitudes prevail, where this is unacceptable some kind of compromise is sought. The biggest risk seems to be that formulation and processing changes made during the transition, from say a 100,000 capsule batch involving possibly 10 to 20 kg of powder to the production batch size of maybe 200 kg powder, may affect bioavailability. The obvious way to avoid, or at least reduce the chance of changes being made at the scale-up stage, is to ensure close contact and understanding between formulation pharmacists and their production colleagues. Current awareness of preferred processing methods must be one of the formulation pharmacist's objectives. The problem is most severe of course for multinational companies where

variations in the availability of raw materials and particular pieces of equipment may cause local difficulties. Nevertheless, even this can be limited by the coordination of formulation attitudes in the centres carrying out development projects. As with so many things, it is largely a communications problem. Another approach to reducing the risk of changes during scale-up is to use highly sophisticated techniques of formulation optimization in the very early stages of development when perhaps only gramme quantities of drug are available. This method is being employed in the field of powder compaction studies by certain companies (eg ICI Ltd), as indicated by recent publications, and entails considerable capital investment.

Some companies adopt a policy in the first phase of developing what are termed "service forms". These are dosage forms produced on a limited development programme to ensure early delivery of material for human trials. This may not be the best general approach although, for various commercial reasons, material is supplied which may not represent a fully optimised formulation and it is accepted that changes may be required at a later date. The most familiar case is that where only very limited stability data is available at the time of CTC submission and a commitment to provision of on-going

stability data is made. Sometimes the follow-up results are not too attractive! However, looking at this problem in the reverse situation, where one is starting production of clinical trial supplies of a product which has been developed elsewhere, it must be said that the resolution of some of the problems is not as simple as it may at first appear. For example our American colleagues' predelection for the Fitzmill as a mill, mixer and granulator has certainly caused difficulties because the Fitzmill is not by tradition a machine in general use in Europe.

Brief mention of the placebo problem is necessary. The Latin word placebo is translated as "I shall please" and in the present context we interpret this to mean satisfying the organiser of a double blind clinical trial that neither the patient nor the clinician can distinguish between active dosage forms and those having no drug content.

In Figure 2 is shown Joyce's summary of the minimal specifications for capsules and tablets to be used in comparative trials.

There are arguments against some aspects of this classification but these are mainly questions of degree.

1. To match perfectly*	2. To match as closely as possible
a) Shape	a) Taste on licking
b) Size	b) Taste on chewing
c) Surface colour	c) Internal colour
d) Surface texture	d) Internal texture
e) Weight	e) Smell
	f) Specific gravity

3. To be free from external distinguishing signs

* Samples must be indistinguishable to a panel of 4 judges

FIGURE 2

MINIMAL SPECIFICATIONS FOR CAPSULES OR TABLETS TO BE USED IN COMPARATIVE TRIALS

(From C R B Joyce, Psychological Factors in the Controlled Evaluation of Therapy, p215-242, in "Psychopharmacology, Dimensions and Perspectives" Editor C R B Joyce, Tavistock, London 1968).

Suffice it to say that in some cases it is not possible to get a close match and recourse is made to some form of "cover up" usually by use of a hard gelatin capsule shell or alternatively by use of the "double dummy" technique. Even using capsules the "blind" cover of a

trial can be ruined by, for example, perception of a delayed bitter after taste. Quality control checks on placebos should include confirmation that the product is a good match with the intended active products and analysis to confirm the absence of the drug.

More frequently clinical trials entail testing the efficacy of a new drug product in comparison with the most effective (or most widely prescribed!) competitor product. Much has been written of the problems of achieving double blind conditions in this situation. A range of factors such as dosages, preferred dosage forms, identifying marks etc. affect the approach to such studies. It may be necessary to prepare comparison dosage forms using the active ingredient of the competitor's marketed product. A key factor in this regard is demonstration of bioequivalence of the competitor marketed product with whatever form of the competitor's drug is used in the trial. Sometimes, of course, it is possible to obtain supplies of unmarked competitor product and to match the company's own drug dosage form with them. In this case it is necessary to demonstrate that the experimental materials are bioequivalent to the dosage form eventually marketed. In some cases where the drug is

known to be readily absorbed it may be possible to satisfy Regulatory Authorities with in vitro drug release data alone.

Another difficulty which has been exacerbated by more recent legislation is the labelling of clinical trial materials. The requirement in the UK is that labels bear the Clinical Trial Certificate number or the Product Licence number in addition to the usual details of administration, origin, Batch Number etc., and in some cases this has caused loss of clarity through overcrowding. A related problem has been the maintenance of double blind conditions where comparison is being carried out between a new drug product and one already marketed and which therefore has a Product Licence Number. This difficulty has been overcome by giving such trials a Trial Identity Number (TIN) which allows fairly rapid identification of the contents of a container should the need arise and meets the requirement that material bear, "such designation as will sufficiently identify the clinical trial".

The inclusion of an expiry date on the label of a clinical trial product is company policy and it would be interesting to learn if this is generally practised. It does, however, cause concern when the stability data

available for the product is limited. We have adopted the principle of careful stipulation of storage conditions on the label together with conservative estimates of shelf life and revision as additional data becomes available. Implicit in this approach is regular monitoring of stability of clinical trial stock and a thorough system of stock control. The possibility of changes occurring in placebo material during storage should not be overlooked.

A few remarks on the location of the clinical trial supplies unit and the relationship with other departments are relevant. The section providing clinical trial materials will usually be located in the pharmaceutical product research and development department. Depending on the size of such a department, clinical trial products will be manufactured exclusively by a section dedicated to this task or some materials may be partly or wholly provided by the formulation scientists involved in their development. Whichever is the case, close cooperation between the various sections is important with exchange of clear documents and information.

In another context, the need for good communications has already been emphasised and the same applies

to the organisation of supply of the correct clinical trial products, in the required quantity at the required time and place. The way this matter may be organised is shown schematically in Figure 3. The importance of exchange of information and theneed for consultation to ensure that the trial is conducted using supplies to meet protocol requirements and conforming to Clinical Trial Certificate specifications is vital : lack of consideration of details such as the need for a break-bar on a tablet at a sufficiently early stage can have far-reaching consequences. It will be noted that orders for despatch of clinical material are initiated by a request from a clinician in Clinical Research Department. In essence, we regard this matter as if a prescription is being written and indeed, we have a system of authorisation for supply based only on the signature of a clinician. Note also the absence of a formal link between Company formulation pharmacists and outside clinical collaborators. There have been suggestions that hospital pharmacists should be more involved in the supply of materials for trials conducted in their hospitals. We see this only increasing the problems : companies do not wish to release new product formulation details and wish to retain control of the supply arrangements using their own staff especially when, as must be apparent in most cases, the drug has

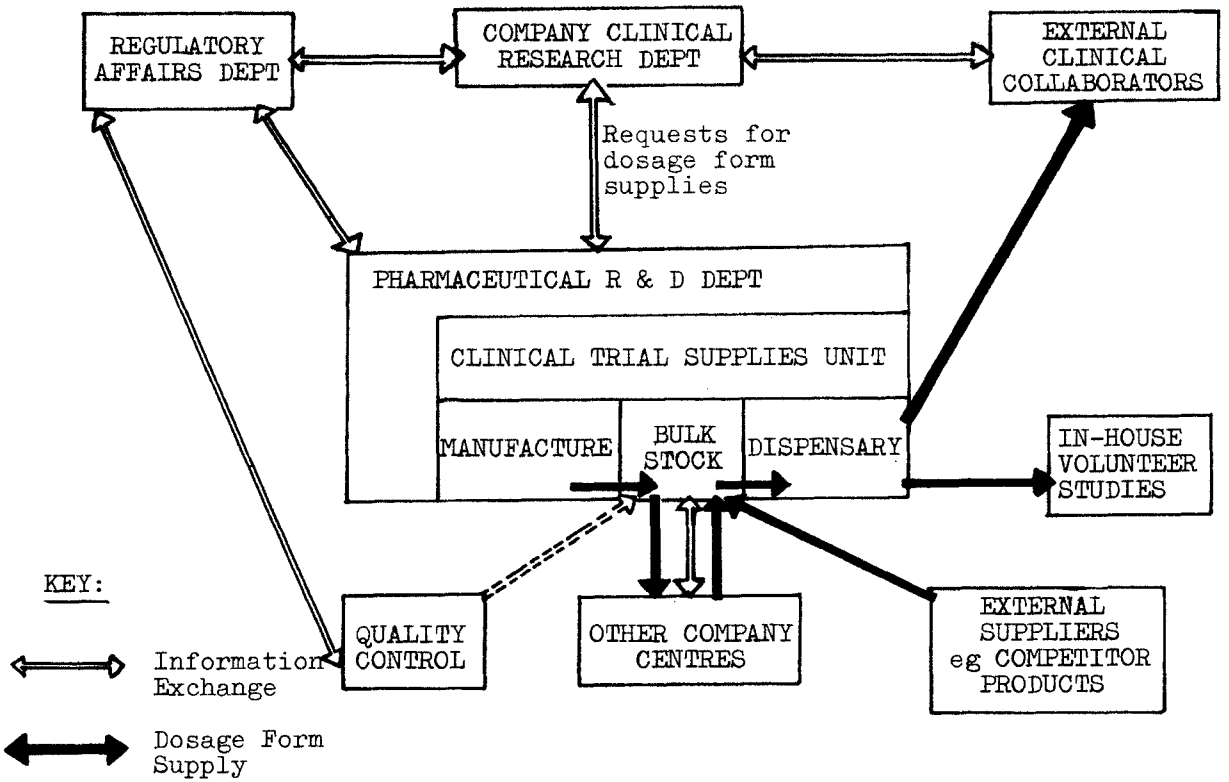

FIGURE 3 In-Company Organisation relating to Clinical Trial Supplies

been sent to the hospital in a dispensed state. It is not unnatural for companies to feel that their staff have the expertise and experience to deal with problems encountered with their experimental drugs and wish to maintain control so that in the event of difficulties they are called upon directly to give any required assistance. The hospital pharmacist has a duty to ensure that his clinical colleagues are using materials which, for example, have not passed their expiry date and of course the hospital pharmacist is in an excellent position to be the guardian of the double blind code. The industry believes too that the hospital pharmacist should be aware of all the trials going on in his hospital, but that trial material is best manufactured, packed and labelled in its own facilities.

In conclusion, some of the more general problems associated with the provision of clinical trial material have been outlined. Some of the problems are magnified in companies working on an international scale with research centres in several parts of the globe. The difficulties are increasing with changing and growing complexities of drug research and the requirements of Regulatory Authorities. The situation demands close cooperation between the various dis-

ciplines involved in drug research and development. The important role to be played by pharmaceutical scientists of high quality in the application of responsible attitudes to the manufacture and supply of clinical trial products cannot be over emphasised.