I would like to comment on certain topics addressed by this session's lecturers illustrating my presentation with examples mostly from personal experiences in the regulatory area of the U.K. pharmaceutical industry. I will try to avoid the peculiarity (in a European context) of extensive data requirements for performance of U.K. clinical trials; these are under review and likely to be rationalized considerably in the near future. In effect, U.K. guidelines have meant that preclinical data in the U.K. have had to be supplied earlier than elsewhere in the drug registration pathway and that much of the clinical research on U.K.-discovered drugs has been carried out abroad. (A figure of 80% was quoted at a recent meeting.) The U.K. authorities have been criticised for tending toward the search for absolute safety and away from the encouragement of new drug development. It was recently stated that 97% of research work carried out by one of the largest U.K. pharmaceutical companies was abortive, largely due to the extensive tests conducted on compounds later abandoned at the early clinical stage. I will come back to this point a little later with reference to costs involved, but I suppose one of my basic pleas is to get drugs into man for testing somewhat earlier in their development.

TOXICITY TESTING

The preclinical guidelines in the U.K., and probably E.E.C., taken as a whole, have been accepted by most responsible pharmaceutical companies although—as I have already implied—with increasing costs to the manufacturer and with considerable time delays. Curiously enough, leaving aside the necessity of certain of the toxicity studies currently required in the U.K., in my experience the
Committee on the Safety of Medicines (CSM) very rarely questions this area of preclinical data submitted. I personally suspect assessors really only look at summary pages and are concerned on a check-list level only. In other words, toxicity reports, prepared at great cost by experts in the field, are very rarely examined thoroughly by similarly qualified individuals in the regulatory authority. In our experience the U.K. CSM concentrated on the clinical evidence submitted, since clinical safety is a long term assessment involving postmarketing surveillance, as has been discussed, perhaps "Committee on Efficacy of Medicines" would be a more appropriate titled followed perhaps by the words, "and on safety of medicines in animals," bracketed in qualification.

The biggest preclinical problem area as far as U.K. regulatory questions are concerned appears to be in chemistry and pharmacy. Without going into specific topics in an area probably not of great interest to anybody here, I think these problems are out of proportion to their actual importance and more closely related to the proportion of pharmacists and allied experts in the regulatory agency. Certainly, I would imagine almost every application made to the U.K. CSM is so questioned, often at a seemingly trivial level. I wonder also how a PLA or CTCA for currently-available Interferon, with a purity of less than 1%, is or will be treated by the U.K. chemistry and pharmacy sub-committee. New concepts of quality assessment and, indeed, safety assessment will be needed for monoclonal antibodies and genetic engineering materials both of which can be produced only in minute amounts with current technology.

Turning to pharmacokinetics, I accept that wherever possible the species studied should mimic human handling of the drug and that such species should be the ones chosen for chronic toxicity testing. As Dr. Griffin has said, drug kinetics in man are not normally investigated before some toxicity testing in animals. I think my company should test earlier in man than it does rather than selecting species for toxicity testing arbitrarily (normally the dog and the rat) with little knowledge of variations in this species' handling of the molecule concerned.

One example of a peculiar species-dependent toxic effect which nearly caused suspension of the drug's development was, I believe, that of sodium cromoglycate in the dog. Problems of cost and availability do detract of course from using the monkey or related species more often. CSM unfamiliarity with more esoteric species prevents their use although I understand the marmoset has proved very useful to the ICI and others. The problem of "which species" has indeed formed the subject of many symposia, and I have nothing useful to add.

Acute toxicity studies are always required in submissions to drug regulatory authorities. Still, I am not convinced the LD₅₀