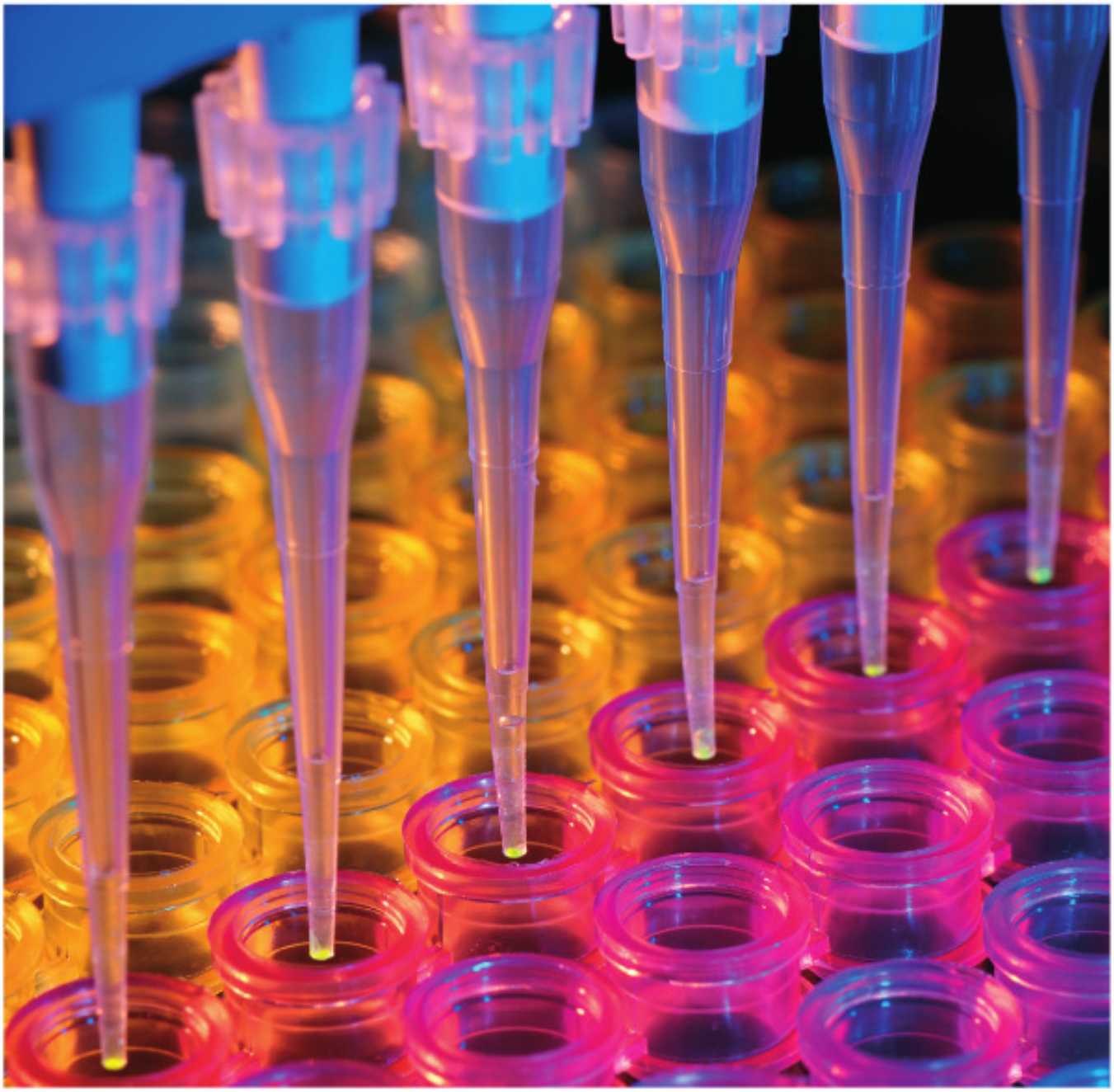
Edited by P A Carson and N Dent

Good Clinical, Laboratory and Manufacturing Practices

Techniques for the QA Professional



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Techniques for the QA Professional

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(iv) Development of isolation, separatory (*e.g.* HPLC or GC) and spectral (*e.g.* MS or NMR) procedures.
(v) Pharmacokinetic studies in animals (*i.e.* work on the kinetics of ADME processes of parent drug and/or major metabolites), including bioavailability studies.
(vi) Toxicokinetic studies (*i.e.* the determination of drug levels in the plasma of animals during toxicology studies).

22.4 AREAS GIVING SPECIFIC PROBLEMS FOR GLP IMPLEMENTATION

22.4.1 Specific Problems Encountered

As has been stated, GLP regulations were drawn up to cover toxicology studies. Drug metabolism and pharmacokinetic studies differ significantly from normal toxicological studies in several aspects. They are concerned with animal studies that are open-ended, without the clearly defined time span of a toxicology study, which has a definite start and finish date.

Radioactive materials, which are inherently unstable due to radio decay, may be available in too small a quantity to permit normal chemical purity testing.

The complex instrumentation used in the performance of drug metabolism, or pharmacokinetic studies and their associated analytical technique, requires specific calibration, maintenance and quality control procedures to be set up.

The drug substance itself may well be destroyed in a study and thus pose the secondary problem of not being able to retain samples.

In the animal species used for drug metabolism and pharmacokinetics, there is often little difference between that of a toxicological study and thus poses a problem for 'justification of the test species'.

22.4.2 Attempts to Resolve the Problems

In view of the problems outlined, a philosophy of GLP in terms of quality standards should be applied to drug metabolism and pharmacokinetics. Certain areas of work may require 'a thought process' to ensure regulatory compliance.

The following examples demonstrate the range and variety of difficulties that can be encountered and give an indication of how good management techniques, good science and GLP can coexist in harmony.

22.5 PROTOCOLS

ADME are not routine procedures, unlike mainstream toxicology and, therefore, protocols may vary extensively from experiment to experiment. It may be that until the conclusion of one piece of work, one cannot draw up a protocol for the next. Hence it is difficult to comply with the current regulatory requirement for detailed protocols. For example, in metabolite isolation a completion date is extremely difficult to predict. Likewise the start date is entirely dependent on the production of radiolabelled material. The date the protocol is supplied and signed by the sponsor also poses a problem. Often contract research companies carrying out studies on behalf of sponsors, submit a protocol duly signed by their staff, but would not necessarily expect to get the sponsor's signature on the final definitive protocol until some time later. Usually verbal agreement is given, a letter of confirmation sent and, once the radiolabelled material is available, the protocol goes forward for final sponsor's signature and the study starts.

Another area of 'non-compliance' surrounds the justification for selection of the test system. In most cases drug metabolism studies identify the likely species for toxicological work. The ADME