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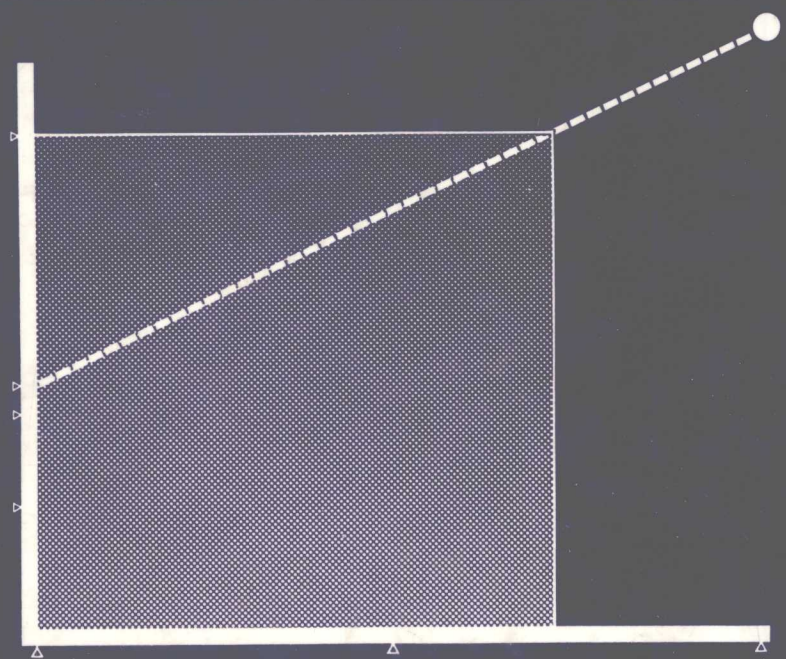
ANALYSIS FOR DRUGS AND METABOLITES

Including Anti-infective Agents



Edited by Eric Reid and Ian D. Wilson

Methodological Surveys in Biochemistry and Analysis, Volume 20

Analysis for Drugs and Metabolites,

Including Anti-infective Agents

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Senior Editor's Preface

The session on assay validation (sect. #**A**) was a highlight of the 1989 Bioanalytical Forum which has given rise to this book. In respect of this and the other Forum material, the Editors have endeavoured, as in the past, to transform what could have been a mere 'Proceedings' volume, inevitably lacking smoothness and quality, into a 'reader-friendly' integrated book. Editorial trimming of fat off the meat, and rendering the content clearer or more informative in places, have been taken in good part by authors concerned.

Over the past decade it has become easier to gain publication texts as well as spoken presentations, especially from staff in the pharmaceutical industry. This is a healthy sign that sound bioanalysis is no longer a 'back-room' product which is taken for granted: the skills and judgement involved are gaining welcome recognition. Regrettably, however, some of the now numerous publications from company laboratories appear not in 'hard' journals but in a new breed of 'throw-aways'; such citations have mostly been excised in the present editing exercise.

The section (#**B**) on anti-infectives, including anti-parasitics and antivirals, is wide-ranging; but comprehensiveness is obviously an unattainable aim (despite editorial 'top-up' at the end of the section), as was likewise the case for therapeutic classes that have featured in past volumes (anti-cancer, psychoactive, cardiovascular and anti-inflammatory drugs). However, articles that seemingly do not match a particular method-development need may nevertheless give guidance or ideas where there is some similarity in analyte or matrix properties to a reader's particular analytical problem. Such analogies in respect of the analyte may also be drawn from the feature-based Analyte Index, which has structural categories, especially relevant to solvent extraction, derivatization and GC detection, that date back to the 1978 volume but are still pertinent although HPLC now predominates as the end-step. The layout of the General Index also follows the pattern used in past volumes, to facilitate entry-searching.

Publishers' publicity for past volumes in the 'Analytical' subseries has not done justice to their usefulness as a reference source. Any reader who is only now becoming aware of this will find a list in a later 'Note' (#**ncC-3**) and may ask the Editor to amplify. Now we have a new publisher, assuring no inordinate delay in publication.

As a traditional book feature, there are 'Notes & Comments' ('**nc**') items which serve partly to give an impression of debate at the Forum and partly as bibliographic reinforcement. Many articles revolve on method-development strategy. This features at the start of the first bioanalytical volume (1976) in an article by R.G. Cooper that still holds good:- 'Development of Analytical Methods: General Philosophy'. One of his points, that a newly developed method needs try-out by those who will use it routinely, is echoed in the present volume, sometimes with the term "reproducibility" although sometimes this term is used as a questionable synonym for "precision". Whilst this Editor sees signs of computerized obsessiveness in present-day validation and quality-assurance policies and, moreover, is a heretic (not alone) as regards the vogue for having an internal standard, he is glad that one sin is now seldom perpetrated, namely the listing of near-nil values as '0' rather than as, say, '<0.1'.

Acknowledgements.- Valued support for the Forum came from U.K. pharmaceutical companies - Beecham, Glaxo and ICI. Many speakers made little or no call on Forum funds. Suggestions for Forum themes came from Honorary Advisers - U.A.Th. Brinkman, J. Chamberlain, H. de Bree, L.E. Martin, J.D. Robinson and R. Whelpton. Thanks are due to certain publishing bodies, as acknowledged where applicable, for permission to reproduce Figs. Vol. 10 (publ. Ellis Horwood) furnished the cover 'logo'.

Conventions and abbreviations.- For temperatures (°), °C is generally implied. Adherence to old-fashioned terms such as 'µg/ml' and 'M' (rather than 'µg.ml^{-1}', mol.L^{-1}) reflects editorial policy. Well-known terms such as GC, HPLC, S.D. and r (correlation coefficient) are used without definition. Other recurring abbreviations, usually listed in the articles concerned, include the following.-

Ab, antibody
EC, electrochemical (detection)
GC detector types: EC, electron-capture; FID, flame-ionization [cf. NMR usage!]; NPD, nitrogen-phosphorus
MS, mass spectrometry (modes include EI, electron impact)
HPLC modes: NP, normal phase; RP, reversed phase:, IE(C), ion-exchange (chromatography)
OPA, *o*-phthaldialdehyde
QC/QA, quality control/quality assurance [samples *implied?*]
RIA, radioimmunoassay
SPE, solid-phase extraction

A plea, with hindsight: shun the term reproducibility *('robustness' or* precision *implied?).*

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25 March 1990

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Contents

The 'NOTES & COMMENTS' ('**nc**' items) at the end of each Section include comments made at the Forum on which the book is based, along with some supplementary material.

Section #A

PRODUCING VALID AND ACCEPTABLE ANALYTICAL RESULTS

#A-1

PROBLEMS AND PITFALLS IN ANALYTICAL REQUIREMENTS FOR PHARMACOKINETIC STUDIES BY THE MEDICINES COMMISSION

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Documentation of analytical methods used for biological studies forming part of a product licence application is often limited to a small paragraph referring to the precision of the method or to a published reference. This contrasts sharply with the reported detailed work-up of analytical methods used for stability studies; this difference is increasing sharply with the need to ensure "essential similarity" of drug substances when applying for product licences for generic products.

Possible reasons for this contrast in approach are discussed, and exemplified by applications which illustrate the point. Details of the information required by the licensing authority are reviewed with emphasis on the pre-analytical process and confirmation of specificity of the method. The increasing requirements for information on the kinetics of different isomers of racemic products are reviewed. The nature of the information is indicated, and proposals for future submissions outlined.

Most new drug applications, whether for a new chemical entity (NCE) or for an alternative formulation of an existing product, contain some pharmacokinetic data. This usually takes the form of data for plasma concentration *vs.* time. Other types of data, such as urine concentrations, are occasionally presented; but this is very infrequent.

When looking at the problems and pitfalls associated with the analytical aspects of such data, it is helpful to keep in mind the use to which the information is put. The Medicines Commission uses it to give reassurance that NCE's are absorbed efficiently, that the proposed dose regimens are appropriate, that the active agent is known and, for generics, that the formulation is as effective as those already on the market. This type of information can be obtained from pharmacokinetic studies by calculation of key

parameters. Amongst these are, for i.v. administration, clearance, volume of distribution, fraction excreted unchanged and main routes of elimination; for oral administration, maximum plasma concentration and time to attain it, area under the plasma concentration/time curve, elimination half-life and absolute or relative bioavailability.

The Committee is not particularly concerned with the analytical methods used to obtain this information. It is very concerned with the reliability of the results presented, because key decisions as to the award of the product licence will be based on this information. The very nature of pharmacokinetic data gives cause for concern when making such decisions. Pharmacokinetic data when presented as the average results for a set of individuals often look respectable, as when the oral bioavailability of two products is being compared. The S.E.M. bars are often omitted because, as some applicants say, this helps to avoid presenting a complex picture. Examination of the individual data in detail can show that there is little inter-subject variability, and indeed the plotted mean values fairly represent the data, or as is more often the case we find a wide range of individual values for C_{max} and T_{max}. It is not uncommon to find that the S.D. is 40-50% of the mean value.

It is the latter type of data that causes problems for the Committee and highlights the role of the analyst since the Committee needs reassurance from the submission that the data are real and not an artefact of the analytical process. Applicants must provide sufficient information in the application to resolve any doubts in this area.

Unfortunately, this is an area which is often given less than adequate coverage in the report; it is unclear whether the quality assurance (QA) department or the product licence department is carrying responsibility for this problem. Many applicants give the validation studies for methods used in stability studies and in product-release specifications in some detail. In contrast, bioanalytical methods often receive a 10-line description with very little validation data, or at worst merely a reference to a published method again without validation data, implying that the literature method worked perfectly in their laboratory. Even in the better applications, which describe the analytical method in detail and give good validation data for the method, it is rare to find, for the whole analytical process, an appreciation which, with detailed consideration, does it justice from the sampling process right through to the presentation of results.