Quality assurance and standardization of empirical trials on drugs and driving
Introduction to the workshop

S.D. Ferrara
Centre of Behavioural and Forensic Toxicology
IML, University of Padova, Via Fallopio 50, 35121, Padova, Italy

Advances in empirical and epidemiological studies have shown that, in addition to alcohol, other drugs, especially psychotropic drugs, can impair mental and physical functions and thus contribute to road accidents (Ferrara, 1987; Compton and Anderson, 1985).

Consistent results by different investigational groups make up a reasonable body of circumstantial evidence for the role of drugs in traffic accident etiology. Experts have also independently concluded that certain commonly used medicinal drugs profoundly impair the performance of particular individuals in specific driving tasks; that large differences exist between the effects of different drugs within the same therapeutic class; and that health care professionals and the driving public are largely unaware of these effects and differences (O'Hanlon and de Gier, 1986).

In empirical research, what drug investigators aim for in modern drug design is the development of drugs with fewer side-effects. As drug manufacturers have recognized that improved quality of life is a strong sales approach to medicinal drug development, new aspects of drug investigations have appeared, together with the important role of empirical research on behavioural side-effects (Hindmarch and Stonier 1989-90; O'Hanlon and de Gier 1986).

For similar reasons, there appears to be at present a trend for international bodies such as the WHO, and other international and national drug regulatory authorities to wish to have performance studies included in the pre-registration testing of any drug likely to affect CNS functioning (Wolschrijn et al., 1991).

The large number of drugs available, the great variation in doses taken and their metabolic fate, the variability between individuals with regard to rates of uptake and elimination, the highly differential effects on the Central Nervous System and, for many drugs, a lack of correspondence between CNS impairment and blood level of the parent drugs, make it necessary to carry out a large number of studies by number of drugs and medicaments.

The latest move in this field is the development of new studies with laboratory tests, simulated driving, and driving in supervised conditions,
accompanied by analysis of drugs and active drug metabolites in biological fluids.

Unfortunately, most of the research carried out so far does not determine the degree of impairment, but merely shows whether or not the drug is impairing. Moreover, not all researches are comparable and easily accessible to the medical profession, and an analysis of available research results would be necessary to fully interpret and translate these data into practical information (O'Hanlon and de Gier 1986). Also, it is not easy to decide which kind of detrimental effects should predominate for a rank order of psychomotor performance impairment, and a review of the literature gives the impression that many empirical studies that may contribute data for categorizing drug effects on driving performance are flawed and that the data-base as a whole is not entirely suitable for this purpose (O'Hanlon and de Gier 1986).

For these and other equally complex reasons, it is universally accepted by experts working in the field that it is possible and desirable to reduce the diversity of research by means of standardization, also considering that:
- the behaviour under investigation must be related to the actual occurrence of accidents;
- the conditions under which the behaviour is examined must correspond to those in which drugs and driving are normally combined.

In spite of several national and international guidelines for the conduct of clinical trials of psychotropic drugs (Muller-Oerlinghansen, 1990), including the so-called "Wittenborn" guidelines and, more specifically, Irving's (1986) proposals, general and specific questions must be still answered.

Similarly, the range of methods at present claimed to be measuring relevant aspects indicates that, so far, no single method or combination has been found which is generally agreed to be adequate for this purpose (Berghaus and Friedel, 1992).

The first step towards a proposal for internationally consistent methodology was taken at the end of the Workshop convened in Padova in October 1991. In particular, the Working Group co-ordinated by de Gier and Laurell agreed upon the outline of recommended methodology stated in Table 1.

These guidelines, explained by de Gier and Laurell with even-minded criticism in Chapter 2 of the book Methodology in Man-Machine Interaction and Epidemiology on Drugs and Traffic Safety (Ferrara and Giorgetti, 1992), are to be understood as a basis for discussion and examination starting from this Workshop on Quality Assurance which is a praise-worthy initiative on the path to the development of international standardization of methodology.
Table 1. MAN-MACHINE INTERACTION.
OUTLINE OF RECOMMENDED METHODOLOGY

Subjects

1. HEALTHY VOLUNTEERS VERSUS PATIENTS
   Inclusion - Exclusion Criteria should provide assurance
   that subjects are suitable for purpose of study

2. COMPOSITION OF SAMPLE
   Subject samples should comprise:
   - Healthy volunteers
   - Men and women
   - Age range found in driving population

Design

1. CONTROL CONDITIONS
   - Placebo
   - Verum

2. DOSES
   - Lowest and Highest to be administered therapeutically

3. DURATION OF TREATMENT
   - Multiple doses until:
     - Steady-state
     - Acute effect stabilized at lower level/tolerance

4. SPECIMEN ANALYSIS
   - Blood
   - Plasma
   - Urine

Performance tests

1. CONSTRUCT VALIDITY
   - Sensitive to drug effect
   - Relevant to driving ability

2. CONTENT VALIDITY
   - Selection of tests as measures of a representative sample
     of independent behavioural functions involved in driving

3. TEST - RETEST RELIABILITY

4. USE OF COMMON SCALE
   - Performance measures must be recorded on common scale

Statistical analysis

1. SELECTION OF RIGHT MODEL
   Drug is hypothesized to have an effect on performance which:
   - differs from
   or
   - is equivalent to effect of Placebo or some other drug

2. CHECK FOR TYPE I - II ERRORS
References


