Muster für

Prüfbericht einer Klinischen Studie Englsich

1 TITLE PAGE

The title page should contain the following information:

- name of the company (other sponsors)
- report title
- protocol number
- trial phase
- study initiation date (first subject enrolled, or any other verifiable definition)
- date of early study termination, if any
- study completion date (last subject completed)
- name and affiliation of signatory investigator, i.e.

(investigator according to Good Clinical Practice (GCP) regulations and Directive 91/507/EEC, part 4, C.1)

- name of company signatory (person responsible within the company - project leader, medical writer, study monitor, statistician - name and business telephone)
- Good Clinical Practice (GCP) compliance
- availability of audit certificates (optional)
- date of report

1.1 TABLE OF CONTENTS FOR THE STUDY

The table of contents should include:

- the volume and page number of each section, including summary tables, figures and graphs,
- a list *and the locations* of appendices, *tabulations and any CRF's provided*.

1.2 LIST OF ABBREVIATIONS AND TERMS

A list of the abbreviations and terms used in the report should be provide. In general, the term should be spelled out and the abbreviation indicated in parantheses at first appearance in the text. Pharmacokinetic constants should be defined in the text. The use of any specific unit system should be defined and the conversion indicated.

2 SYNOPSIS

A synopsis that summarises the study should be provided *(cf Annex I of the guideline for an example, page 22). The synopsis should include numerical data to illustrate results, not just text or p-values.*

3 INVESTIGATORS

A list of the investigators and their affiliations *(with the signatures if required by applicable regulations)* should be provided in an appendix *(cf Annex II of the guideline, page 24)*[1].

Comment 1: Commission Directive 91/507/EEC of 19 July 1991, modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products, part 4, C.

4 INTRODUCTION

The introduction should contain a brief statement of the general intent and design of the trial (no more than two pages) describing the rationale for performing the study. It should provide concise details on the back-

ground of the drugs and the disease and place the study in proper context within the drug's clinical developement.

5 STUDY OBJECTIVES

A statement of the specific objectives of the study should be provided. In addition to the primary objective, any secondary objectives and subgroup hypotheses should be stated explicitly. It should be noted whether any changes to the objectives were formulated during or after completion of the clinical phase of the study.

6 INVESTIGATIONAL PLAN

6.1 STUDY DESIGN AND PLAN - DESCRIPTION AND RATIONALE

6.1.1 Overview and Justification

A brief overview of the key elements of the study should be provided. If other submitted studies used an essentially identical protocol, this should be noted and any differences described. It may be possible in that case to eliminate most of the description of the investigational plan.

The following is a checklist of elements to consider for inclusion in this section:

- prospective/retrospective
- comparative group(s), investigational and comparator products used and their dosages
- level of blinding (e.g., parallel group, indicating number of arms/cross-over/cohort)
- method of assignment to treat
- subject population (i.e., the indication) and the number of subjects
- sequence and duration of study periods
- any safety, data monitoring or special steering committees
- any interim analyses (and justification)

Where appropriate, a figure illustrating the study design should be provided.

Some discussion should be included here, *or in Section 11*, in which the choice of the study design and the choice of the control groups are justified, if this is not obvious.

6.1.2 Protocol Amendments

Any important change in the protocol or conduct of the study instituted after the start of the study should be described, giving the time(s) and reason(s) for the changes. Discuss any possible implications for the conduct and interpretation of the study in the appropriate section of the study report.

Comment 2 Known or potentil problems associated with the design chosen, and its suitability for the specific claims under study, should be discussed. For example, for a crossover design, there should be consideration of the likelihood of spontaneous changes in the disease during the study, and the need (or lack of need) for reestablishment of baseline effects to show that they are inconsequential. For a positive (active) control study, there should be evaluation of the appropriateness of the control and of the dose employed (e.g., regulatory approval of the treatment for the condition studied, literature support for effectiveness), and of whether the study was intended to show a difference between treatments or show similarity between them; if intended to show the latter, the present study design and patient population should be compared with previous studies of the control agent that were successful in showing effectiveness compared to placebo. The limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, etc.) and deserve particular attention. (FDA - 6(b))

6.2 ETHICS

6.2.1 Ethics Committee

It should be confirmed that the study and any amendments were reviewd by an Ethics Committee. If appropriate, the composition of the committee should be described in an appendix.

6.2.2 Declaration of Helsinki

It should be confirmed that the study was conducted according to the principles of the Declaration of Helsinki and its amendments.

6.2.3 Subject Information

The following subject information, *as described in the protocol*, should be included:

- how and when (in relation to subject enrollment) informed consent was obtained.

provisions for data protection, the maintenance of confidentiality and the information given to the subject with respect to these issues.

6.3 STUDY POPULATION

The study population should be specified with detail appropriate to the study objectives (patients/healthy subjects), identifying the source of subjects and describing the techniques used for subject recruitment.

6.3.1 Inclusion

The inclusion criteria (preadmission and admission), including age, sex, ethnic group, diagnostic admission criteria and prognostic factors should be specified and justified.

6.3.2 Exclusion

The criteria for exclusion at entry into the study should be specified and justified, as appropriate.

6.3.3 Withdrawals

The criteria for withdrawal during the study should be specified and the *criteria for evaluation of data from such patients described*.

6.3.4 Sample Size - Number of Subjects Planned

The number of subjects planned for inclusion should be stated. Provide a rationale for the planned number of subjects, preferably in terms of power to detect a difference in the primary variable or endpoint.

6.4 TREATMENTS

6.4.1 Treatments to be Compared

The treatments to be compared should be completely identified by name of drug, marketing formulation, route and mode of administration, dose, dosage schedule, and treatment period.

In controlled studies, specify whether the control group received:

- no treatment
- a placebo
- *dose comparison current control*
- another medicinal product of known effect
- treatment other than therapy with medicinal products

The precise treatment (drug, control) used during the study periods of the study (placebo baseline, randomised treatment, withdrawal, etc.) should be completely clear.

6.4.2 Identity of Test Materials

A description of the investigational medicinal product(s), including test medication(s), active comparator(s) and placebo, should be provided.

Any modification of active control drugs from their usual commercial state should be noted, and the steps taken to assure that their bioequivalence is unaltered, should be described.

In an appendix to the report, provide the batch/serial number of treatment(s) to be compared, a description of the test material formulation and content, its external appearance and analytical documentation (e.g., batch certificate, certificate of analysis).

6.4.3 Dose Selection and Timing

The dose and dosage schedule of the investigational medicinal product(s) and comparator(s) should be described. Describe methods of determining dose response (e.g., fixed drug/dose regimens, titration/back-titration schedules).

Specify the timing of dose, including when a dose should be administered in relation to meals.

6.4.4 Methods of Assigning Subjects to Treatment Groups

In the text of the report, the methods used to randomise subjects to treatment groups should be described.

If randomisation is not used, it is important to explain how other techniques, if any, guarded against systematic selection bias.

For a historically controlled trial, it is important to explain how the particular control was selected and what other historical experiences were examined, if any, and how their results compared to the control used.

In an appendix, provide a table with the randomisation codes, subject identifiers and treatment assignments (broken down by centre for multicentre studies, see Appendix 15.1.6).

6.4.5 Blinding

Procedures for blinding should be described. If blinding was considered unnecessary to reduce bias or was not feasible, this decision should be justified and its implications discussed.

The specific procedures used to carry out blinding and the measures taken to assure that drug or comparator were indistinguishable (e.g., shape, smell, taste, colour, etc.) should be described.

The circumstances in which the code would be broken should be specified and those who had access to subject codes identified.

If some members of investigational team (e.g., pathologist, technical staff) were allowed to be unblinded, the means of shielding other investigators should be explained.

In an appendix to the report provide packaging and labelling documentation for blinding, e.g. double dummy techniques, as well as identify of test materials, if appropriate.

6.4.6 Concomitant Therapy

State which concomitant therapies were allowed and which were desallowed by the protocol. Describe how concomitant therapy was recorded.

6.5 Criteria for Effectiveness

The criteria for the assessment of effectiveness should be described, based on primary and secondary effectiveness variables or variables derived from them. *If possible*, this should include a definition of the effectiveness threshold which is considered as clinically meaningful.

6.6 Effectiveness and Safety Variables

If any of the effectiveness or safety assessments is not standard, i.e., widely used and generally recognised as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), its reliability, accuracy and relevance should be documented. It may be helpful to describe alternatives considered but rejected.

It is also usually helpful to display graphically the frequency and timing of effectiveness and safety measurements; visit numbers and times should be shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret).

6.6.1 Effectiveness and/or Pharmacodynamics[3]

All pharmacodynamic variables assessed should be described, including information on how each variable was measured and recorded. The methods used and their consistency and reliability should be justified. Describe the timing of measurements, especially in relation to drug administration. If effectiveness is to be assessed in terms of categorical ratings, numerical scores, etc., the criteria used for point assignment (e.g., definitions of point scores) should be provided. For multicentre studies, indicate how methods were standardised.

If anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g., a committee to review X-rays or ECG's or to determine whether the subject had a stroke, acute infarction, or sudden death) the person or group should be identified. The procedures, including means of maintaining blindness, centralising readings and measurements, should be described fully.

Comment 3: The primary measurements and endpoints used to determine effectiveness should be clearly specified. Although the critical effectiveness measurements are often obvious, when there are multiple variables, or when variables are measured repeatedly, the protocol should identify the primary ones, with an explanation of why they were chosen, or designate the pattern of significant findings that would be interpreted as supporting effectiveness. If the protocol did not identify the primary variables, the study report should explain how these critical variables were selected (e.g., by reference to publication) and when they were identified (i.e., before

or after the study was completed), and discuss the need, for statistical adjustments of type I error criteria for multiple comparisons. (FDA - 6 (j))

6.6.2 Pharmacokinetics

When relevant, describe the pharmacokinetic variables measured. Describe and justify sample collection times and periods, especially in relation to the timing of drug administration, and comment on possible effects of food, posture and concomitant medication/alcohol/caffeine/nicotine. Specify the biological sample measured, and describe the method used. Refer to published and/or internal assay validation documentation for methodological details.

6.6.3 Safety

6.6.3.1 Adverse Events

The methods used to

- record adverse events (e.g., open questioning, checklists, questionnaires)
- deal with any complications (including procedures for follow-up)
- report adverse events, specifying the reporting procedure and time limits

should be described.

If safety is to be assessed in terms of categorical ratings, numerical scores, etc., the criteria used for point assignment (e.g., definitions of point scores) should be provided. For multicentre studies, indicate how methods were standardised.

6.6.3.2 Clinical and Laboratory Tests

Any clinical and laboratory tests performed should be described with their timing and duration in relation to drug administration. Describe the sample assay methods (refer to published methods when available), the techniques used to standardise or compare results in multicentre studies and the methods used for evaluation (i.e., mean or median values at specified times, trends, out of range values, etc.).

List separately any laboratory variables that were selected for special evaluation because of anticipated pharmacological or toxicological effects of the drug(s) under study.

Any variables that were determined but are not discussed in detail should be clearly identified (e.g., electrolyte levels in seriously ill infected subjects).

6.7 Study Procedures and Flow Chart

6.7.1 Schedule of Assessment

The timing of the clinic visits and the measurements performed at each visit should be presented. Clearly differentiate between parameters used to assess efficacy and those used to assess safety. Displaying this information in the form of table or flow chart *(cf Annex III of the guideline, page 25)* is usually helpful.

6.7.2 Procedures at Each Visit

The assessments made at the screening visit to determine subject eligibility for the trial should be described. If a run-in period was incorporated into the design, describe the key assessments made during this period and the criteria for determining entry into the randomised treatment period. Describe completely the assessments made during the treatment period with details of their timing in relation to drug intake, and assessments performed at follow-up.

6.8 Data Quality Assurance

It should be confirmed that the study was conducted according to the principles of Good Clinical Practice as specified in the appropriate regulations and in the (company) standard operating procedures reflecting these regulations.

The quality assurance and quality control systems implemented to assure the quality of the data should be described in brief.

Refer to independent GCP compliance and quality systems auditing, if appropriate.

6.9 **Statistical Analysis** (GUIDANCE FOR SECTION 7.9, SEE ANNEX IX OF THE GUIDELINE, PAGE 32)

This section should contain all the important information from any statistical appendix provided. The language used should be such that reviewers who are not staticians can understand the general approach. *A detailled account of, and justification for, the statistical methods used, and the individual analyses performed, should be given in the statistical appendix (15.1.9).*

6.9.1 7.9.1 Sample Size Issues

The statistical rationale of the number of subjects recruited in terms of power to detect differences in the primary end-point should be described. Discuss all the other parameters of interest. Clearly distinguish between primary and secondary study objectives[4].

(N.B. This section might be placed instead under Section 7.3)

6.9.2 Comment 4: For a positive control study intended to show that a new therapy is at least as effective as the standard therapy the sample determination should specify a "delta value", a difference between treatments that would be considered clinically meaningful. A Difference smaller than this delta would therefore indicate that the new therapy was clinically equivalent to the standard therapy. The power to detect a treatment difference of magnitude delta or greater should be given. (FDA - 7 (b))

6.9.3 Baseline Comparability of Treatment Groups

For controlled trials, the methods used to compare the treatment groups at baseline should be described.

6.9.4 Planned Analyses

The handling of withdrawals and missing data should be described. Define violations of and deviations from the protocol and describe how these were handled.

Describe the statistical analyses planned in the protocol, together with a justification for any changes made during or after the trial. In case of any unplanned analyses, describe and justify their limitation. The analysis of any endpoints that are not fully defined in the protocol should be justified. Primary, secondary and exploratory analyses should be clearly distinguished. In randomised, controlled studies there should be a comparison of the outcomes of subjects in the group to which they were randomly assigned (intention to treat, *or "all randomised patients with data")* as well as the analyses planned in the protocol.

Provide a brief summary of the statistical techniques used, including adjustments made for covariates (demographic or baseline measurements, concomitant therapy, etc.) and multiple comparisons. Multicentre studies should always include a test of the treatment be centre interaction.

6.9.5 Multiple Endpoints

False positive findings increase in frequency as the number of significance tests (number of comparisons) performed increases. If there is more than one primary endpoint (outcome variable), or if there are multiple treatment groups, or subsets of the subject population being examined, statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why they are considered unneccesary.

6.9.6 Interim Analyses

Any interim analyses carried out should be described, distinguishing those that were not planned in the protocol. Distinguish between those analyses with the potential to terminate or alter the conduct of the study from those carried out for administrative purposes only. Describe the role of any independent data monitoring committee. Ideally, analyses undertaken for such a committee should be planned and described in the protocol. Any interim analyses undertaken should be described with particular reference to any steps taken to prevent influencing the conduct of the study. State whether any statistical adjustment is necessary in the final analysis. If an interim analysis is being reported, state whether any further analyses are planned.

7 STUDY SUBJECTS

7.1 DISPOSITION OF SUBJECTS

In figures or tables in the body of the text of the report, provide a summary of the number of subjects who were screened, entered, excluded and who completed and/or discontinued each phase of the study. The subjects should be grouped by treatment and disposition *(cf Annex IV of the guideline, p 26)*[5].

In an appendix (Appendix 15.2.1) listing of individual subjects data, broken down by centre in multicentre studies, should be provided as follows:

- subjects included, fulfilling the inclusion criteria, and/or completing each period of study, grouped by treatment assignment
- subjects withdrawn prematurely from the trial and the reasons for such withdrawal.

7.2 PROTOCOL DEVIATIONS

All important deviations from the study or from any amendment to the study protocol should be described.

In the body of the text, protocol deviations should be appropriately summarised distinguishing the following groups of subjects:

- those who entered the study even though they did not satisfy the entry criteria
- those who developed withdrawal criteria during the study but were not withdrawn
- those who deviated from other requirements of the protocol in an important way. (The criteria for this judgement must be stated and satisfied.)

Important protocol deviations should be described by centre and differences between centres discussed.

In an appendix, provide a listing of important individual protocol deviations, broken down by centre for multicentre studies.

Comment 5: There should be a clear accounting of all patients who entered the study. The numbers of patients who entered and completed each phase of the study, or each week/month of the study (a flow chart is often helpful), should be provided, as well as the reasons for all post-randomisation discontinuations, grouped by treatment assignment and by major reason (lost to follow-up, adverse experience, poor compliance etc.). There should also be a patient identifier, the reason for leaving, the treatment (drug and dose), and the duration of treatment before participation ended. Whether or not the blind for the patient was broken at the time he left the study should be noted. It may also be useful to include other information, such as critical demographic data (age, sex), concomitant medication, and the major response variable(s) at termination. (FDA - 8)

7.3 DEMOGRAPHIC AND BASELINE FEATURES

The demographic and baseline characteristics of the subjects should be described, i.e.:

- age
- sex
- race
- height
- weight
- disease factors: specify entry criteria (if not uniform)
- duration and severity
- baseline values for critical clinical measurements
- concomitant illness
- relevant previous illness (e.g., renal, hepatic, cardiac)
- concomitant treatment
- relevant previous treatment
- other relevant variables (e.g., smoking, alcohol intake)

The data on the entire subject sample should be given first. This should be followed by demographic and baseline data on different groups:

A) Effectiveness

- intention-on-treat
- per protocol
- defined subgroups (e.g., compliance, concomitant disease/therapy or demographic/baseline characteristics)

B) Safety

- intention-on-treat
- defined subgroups

A flow diagram showing the relationship between the entire sample and the different groups should be provided.

In general, safety analyses will be performed on the entire sample. If any subjects are not eligible for safety analysis (e.g., withdrawal of consent before receiving first dose), this must be clearly stated.

Analyse the comparability of the treatment groups overall, between the specific data sets analysed, and also between centres in a multicentre study.

In an appendix to the report, provide listings of all relevant demographic and baseline data and of all concomitant medication for individual subjects (broken down by centre for multicentre studies).

8 EFFECTIVENESS EVALUATION

Important group mean data (e.g., demographics, baseline characteristics, primary and secondary effectiveness variables) should be presented in figures or tables in the body of the report.

All relevant individual subject data should be available in listings (broken down by centre in multicentre studies), which will only be supplied on request as appendices to the report. The various listings should contain the following:

- all data included in the analyses
- all data relevant to the results of the analyses
- demographics, dosage, compliance, concomitant treatment/disease)
- all data specifically excluded from the analyses (with reasons)

Use a format that allows easy comparison between the different treatment groups and between centres.

Individual ("by subject") data may be presented in figures or tables in the text of the report if considered helpful in the overall evaluation, or for specific issues (e.g., time course of events, relationship of events to the study drug or concomitant therapy).

8.1 DATA SETS ANALYSED

An "intention-to-treat" analysis including all randomised subjects should be performed *in addition to the analyses planned in the protocol*. When subgroup or "per protocol" analyses are presented, the characteristics of the data sets analysed should be clearly described. State also when and how inclusion/exclusion criteria for the analyses were developed, relative to study completion (if not already defined in the study protocol).[6]

Listings of all subjects and data excluded from the analyses (broken down by centre

for multicentre studies) should be provided in an appendix (15.2.1.2).

Comment 6: Exactly which patients are included in the effectiveness analysis should be precisely defined, e.g., all patients with an effectiveness observation or with a certain minimum number of observations, only patients completing the trial, all patients with an observation during a particular time window, only patients with a specific degree of compliance, etc. It should be clear, if not designed in the study protocol, when, relative to study completing, and how, inclusion/exclusion criteria were developed. There should be a tabular listing of all visits excluded from the effectiveness analysis. The reasons of exclusions should also be analysed for the whole treatment group over time. (FDA - 9 (a))

8.2 NUMBER OF SUBJECTS IN EFFECTIVENESS EVALUATION

State the number of subjects in the effectiveness analysis, with a cross-reference to section 8.3. (It may be appropriate to describe the demographic and baseline characteristics of subjects in the effectiveness analyses in this section rather than in section 8.3.)

8.3 EFFECTIVENESS RESULTS

8.3.1 Analysis of Effectiveness

Treatment groups should be compared for all critical measures of effectiveness (primary and secondary endpoints; pharmacodynamics)[7]. Present the results of all analyses contemplated in the protocol and discuss the implications of all withdrawals, dropouts and protocol violations. An "intention-to-treat" analysis should always be performed on all randomised subjects. Analyse the time course of the response (if possible) and also the reasons for withdrawals and dropouts over time.

For a multicentre study, analyse and compare the results from individual centres and discuss any important differences.

Describe and analyse any important differences in measurements or assessments (e.g., discrepancies between investigator, sponsor and expert committee).

Statistical significance should be distinguished from clinical significance when relevant.

Comment 7: Analyses based on continuous variables (e.g., mean blood pressure or depression scale score) and categorical responses (e.g., proportion of patients achieving cure of infection) can be equally valid, ordinarily both should be presented if both were planned and are available. Even if one variable (e.g., in a blood pressure study, supine blood pressure at week x) receives major attention, other reasonable measures (e.g., standing blood pressure and blood pressures at particular times) should be assessed, at least briefly. In addition, the time course of response should be analysed, if possible. For a multicentre study, data display and analysis of individual centres should be included to give a clear picture of the results at each site, especially the larger ones. If any critical measurements or assessments have been made by more than one group (e.g., both the investigator and an expert committee may offer an opinion on whether a patient had an acute infarction), overall differences between the ratings should be shown, and each patient having disparate assessments should be identified. The assessments utilised should be clear in all analyses. (FDA - 9 (c))

8.3.2 Subgroup Analysis

Subgroup analysed must not be used to try to salvage an otherwise inconclusive study.

If the size of the study permits, relevant demographic or baseline value-defines subgroups should be examined for unusually large or small responses and the results presented, e.g., comparison of effects by severity groups, by age, sex, or race, or by history of prior treatment with a drug of the same class.

With respect to concomitant therapy (see 8.3), it might be relevant to distinguish the following:

- treatments given within a specified time period, but discontinued before study entry
- treatments given before study entry and continued during the study
- treatments initiated during the study

In an appendix, data listings of concomitant treatment should be provided.

8.4 DOSE RESPONSE/BLOOD LEVEL-RESPONSE RELATIONSHIP

Describe the actual dosage received in studies in which the dose was given preferably according to body weight or body surface area (for children). If possible, analyse and describe blood level-response and dose response relationships *where these are considered important.*

8.5 DRUG-DRUG AND DRUG-DISEASE INTERACTIONS

If the size of the data base allows:

- describe any apparent relationship between response and concomitant therapy
- describe any apparent relationship between response and past and/or concurrent illness.

8.6 EFFECTIVENESS CONCLUSIONS

The important conclusions concerning effectiveness, distinguishing between the primary and any secondary objectives of the study, should be concisely described.

9 SAFETY EVALUATION

Analysis of safety related data can be considered at three levels, first, the amount of exposure (dose, duration) should be examined to determine the extent to which safety can be assessed from the study. Second, the more common adverse events, laboratory test changes, etc. should be identified, classified in some reasonable way, compared for treatment groups, and analysed, as appropriate, for factors that may affect the frequency of adverse reactions, such as time dependence, relation to demographic characteristics, relation to dose or blood level, etc. Finally, serious, but less common, adverse events should be identified, usu-

ally by close examination of patients who left the study prematurely because of an adverse event or who died.[8]

9.1 Safety Population and Extent of Exposure

9.1.1 Number of Subjects in Safety Analysis

State the number of subjects in the safety analyses, with a cross-reference to section 8.3. (It may be appropriate to describe the demographic and baseline characteristics of subjects in the safety analyses in this section rather than in section 8.3.)

9.1.2 Total Drug Exposure

Some appropriate measures of drug exposure should be provided in the report, by treatment group, e.g.:

- the number exposed to at least one dose
- mean (median) dosage during the completed treatment period
- mean (median) dosage at specified visits
- number and *sex distribution* of subjects reaching specified dose levels
- number and *sex distribution* of subjects completing specified periods

Dosage should be described either in absolute terms or as milligrams per kilograms body weight, as appropriate.

comment 8: It is not intended that every adverse event be subjected to rigorous statistical evaluation. It may be apparent from initial display and inspection that a significant relation to demographic or other baseline features is not present. Adverse events that are relatively important (those that lead to discontinuation or dose changes or are characterised as severe) deserve closest attention. (FDA - 10.B.4)

9.2 Adverse Events (AEs)

The definition of adverse events and serious adverse events used in the study should be stated in the report, if these are not specified in the protocol. The methods used to identify adverse events (e.g., spontaneous reporting/questionnaire/checklist) should be described in section 7.6.3.

9.2.1 Display and Analysis of Adverse Events

All adverse events in all treatment groups must be reported, whether or not considered related to treatment.

If preferred terms are used, a glossary linking the preferred terms to the reported terms should be provided in an appendix.

Summary tables provided in the report should include:

- all adverse events in each treatment group, described by body system
- all serious and all severe adverse events, by treatment group
- all adverse events leading to changes in dosage or withdrawal, by treatment group

The tables can also divide the adverse events into those considered related to drug use and those considered not related.

So that is possible to analyse and evaluate the data in these tables, it is useful to identify each patient having each adverse event, as grouped in the table, by individual patient number, for some or all of the controlled trials. An example of such a tabular presentation is given in the annex VII to this guideline, page 29.

If this presentation is utilised, it may be useful also to provide the table without the patient identifying numbers for quicker reference; treatment and control groups could be shown on the same page. If both tables are used, the latter should be included in the main report, the former in an appendix.

In some cases it is useful to give the number of patients who had any adverse event or no adverse event. Patient and identification numbers need not be listed for these categories. FDA - 10.b.2

Provide additional summary tables, if relevant, illustrating any relationship between adverse events and subjects variables:

- dose or duration of treatment
- demographic or background characteristics

- past or intercurrent illness
- blood levels or drugs
- possible drug interactions, etc.

Individual subject listings for all adverse events should be provided as an appendix to the report (15.2.1.5). The content and format of these listings are described in an annex to this guideline *(Annex V to the guideline, page 27)*.

9.2.2 Overall Adverse Event Evaluation

The overall pattern of adverse events should be described by treatment, grouped by body system, in the report. Adverse event terms that probably present the same event should be grouped. Include also, if relevant, an analysis of frequency, intensity, seriousness and possible causality, clearly identifying adverse events leading to dosage change.

9.2.3 More Common Adverse Events

The overall pattern of more common adverse events should be described in the report (as in 10.2.2 above). The frequency, incidence, prevalence cutoff should be clearly stated.

9.2.4 4 Deaths, Serious Adverse Events, and Adverse Events Leading to Withdrawal[9]

The overall pattern of serious adverse events and events leading to withdrawal should be described in the report (as in 10.2.2 above). Provide a brief narrative *in the text* describing the circumstances of all deaths (and other serious adverse events, if relevant), unless there are good reasons not to (e.g., life threatening illness under treatment).

More detailled Case Summaries for all subjects with serious adverse events and deaths should be provided in an appendix (see 5.3.1). The content and format of these summaries are described in an annex to this guideline *(Annex VI of the guideline, page 28)*.

Comment 9 ICH2. Clinical safety data management. Definitions and standards for expedited reporting.

9.2.5 Laboratory Variables

9.2.6 Display and Analysis of Laboratory Variables

The results of all laboratory tests should be summarised in the report. Any laboratory changes that were considered serious adverse events or that resulted in withdrawal should be described in section 10.2.4.

Summary tables or graphs *of selected laboratory variables* should also be provided in the report, if relevant to illustrate a potentially important observation. These might include:

- mean (or median) values over time
- the range values and the number abnormal (high and low) at each time
- the proportion of subjects whose values deviated from normal (high and low) by a predefined amount (e.g., as specified in the protocol)
- shift tables indicating the number of subjects with low, normal and high values at *baseline and other* appropriate times
- graphs comparing baseline values with subsequent values

Data should be grouped by treatment and, in multicentre studies, by centre *if relevant*. In an appendix (15.2.1.5), listings of individual abnormal laboratory data (by organ system. e.g., liver function tests; by treatment; by centre; by subject) should be provided. Each row should represent one subject visit, and the columns should include the laboratory data and other relevant information (e.g., dose, timing, visit number, concurrent illness, other drug treatment, reference range).

9.2.7 Clinically Important Laboratory Changes in Individual Subjects

Clinically important changes in laboratory variables in individual subjects should be described in the report, noting time of onset, magnitude, action taken, outcome etc. as required to provide a judgement on the possible relationship to treatment.

9.3 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER SAFETY VARIABLES

Vital signs and other physical findings should be analysed and presented in a similar way to laboratory variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the obsevation described. Particular attention should be given to changes not evaluated as effectiveness variables and to those considered to be adverse events.

9.4 SAFETY CONCLUSIONS

The overall safety evaluation for the study drug(s) should be reviewed, with particular attention to events resulting in changes of dose, serious adverse events, events resulting in withdrawal and deaths. Any subjects or subject group at increased risk should be identified. Describe also the implication of the safety evaluation for the use of the drug in the indications claimed, and in future studies. If appropriate, adverse events and changes in laboratory variables which are considered likely to be adverse drug reactions might be identified.

10 DISCUSSION

The discussion should not simply repeat the description of results or introduce new results. Discuss any known or potential problems with the study design, and its suitabilility for the purpose of the study, if not already covered in section 7.1.1. Similarly, discuss any known or potential problems with the study population, and its suitability for the purposes of the study. Describe and justify the rationale for the choice of dose. Describe the consequences of withdrawals, dropouts, etc. and their effects on the statistical validity of the analyses performed.

Clearly identify any new or unexpected findings and comment on their significance. Discuss the clinical relevance of the results, identify any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies.

11 OVERALL CONCLUSIONS

Describe briefly the overall conclusions concerning effectiveness and safety, related specifically to the objectives of the study as stated in section 6.

12 SUMMARY TABLES, FIGURES AND GRAPHS REFERRED TO IN TEXT

The demographic, effectiveness and safety data should be presented, if appropriate. Use figures to visually summarise the important results or to clarify results that are not easily understood from tables.

Key results should be presented in tables and figures incorporated into the text of the report.

13 REFERENCE LIST

A list of articles from the literature pertinent to the evaluation of the study should be provided. Copies of important publications should be attached in an appendix (15.10 and 15.1.11). References should be stated in accordance with the internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" of the system used in "Chemical Abstracts".

Publications in a language other than English should be accompanied by an English translation of the abstract.

14 APPENDICES

This section should be prefaced by a full list of all appendices available for the study report. Some of the following appendices will be submitted with the report and others will be provided only on request, depending on regulatory requirements.