THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PART IV: CLINICAL DOCUMENT

SECTION A. TABLE OF CONTENTS

A table of contents for the filed application should be provided.

SECTION B. CLINICAL OVERVIEW

PREAMBLE

The Clinical Overview is intended to provide a critical analysis of the clinical data in the ASEAN Common Technical Dossier (ACTD). The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyze the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should:

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.
- provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage risks.
- address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved.
- explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them.
- explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the

Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or Clinical Study Reports are encouraged.

TABLE OF CONTENTS FOR THE CLINICAL OVERVIEW

DETAILED DISCUSSIONOF CONTENT OFTHE CLINICAL OVERVIEW SECTION

1. Product Development Rationale

The discussion of the rationale for the development of the medicinal product should:

- identify the pharmacological class of the medicinal product.
- describe the particular clinical/pathophysiological condition that the medicinal productis intended to treat, prevent, or diagnose (the targeted indication).
- briefly summarise the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied.
- briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme.
- note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced.

2. Overview of Biopharmaceutics

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure

3. Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the pharmacokinetic (PK), pharmacodynamic (PD), and related *in vitro* data in the ACTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasise unusual results and known or potential problems, or note the lack thereof. This section should address:

- pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.
- pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.
- interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies.

4. Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be considered:

- relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed.
- implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.
- for non-inferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).
- statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints).
- similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.
- observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).

- for products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
- data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.
- the clinical relevance of the magnitude of the observed effects.
- if surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
- efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

5. Overview of Safety

The purpose of this section is to provide a concise critical analysis of thesafety data, noting how results support and justify proposed prescribing information. A critical analysis of safety should consider:

- adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
- special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
- relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
- the nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace shouldbe explicitly discussed.
- common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or othermembers of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.
- serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for testdrug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.
- similarities and differences in results among studies, and their effect upon the interpretation of the safety data.
- any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
- relation of adverse events to dose, dose regimen, and treatment duration.

- long-term safety (E1a).
- methods to prevent, mitigate, or manage adverse events.
- reactions due to overdose; the potential for dependence, reboundphenomena and abuse, or lack of data on these issues.
- world-wide marketing experience. The following should be briefly discussed:
  - the extent of the world-wide experience,
  - any new or different safety issues identified,
  - any regulatory actions related to safety.

6. Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option; and should clarify the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

- the efficacy of the medicinal product for each proposed indication.
- significant safety findings and any measures that may enhance safety.
- dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
- efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.
- data in children in different age groups, if applicable, and any plans for a development programme in children.
- any risks to the patient of known and potential interactions, including food-drug and drug-drug interactions, and recommendations for product use.
- any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery.

Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include:

- the drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.

- the proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.
- safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

SECTION C: CLINICAL SUMMARY

PREAMBLE

The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Clinical Study Reports of this part may not be required for NCE, Biologics, Vaccines, and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who wishes to obtain such Clinical Study Reports should request for additional documentation.

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the ASEAN Common Technical Dossier. This includes information provided in Clinical Study Reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Clinical Study Reports and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the ACTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

TABLE OF CONTENTS FOR THE CLINICAL SUMMARY

DETAILED GUIDANCE ON ITEMS OF THE CLINICAL SUMMARY

1. SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and *in vitro* dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

1.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutic studies should generally be provided (see Appendix 1), together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important *in vitro* or *in vivo* data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the ICH E3 synopsis.

References or electronic links to the full report of each study should be included in the narratives.

1.3 Comparison and Analyses of Results across Studies

This section should provide a factual summary of all *in vitro* dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarise the findings in text and tables (see Appendix 1) and should consider the following:

- evidence of the effects of formulation and manufacturing changes on *in vitro* dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, pharmacodynamic (PD) studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.
- evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).
- evidence of correlations between *in vitro* dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.
- comparative bioavailability, including BE conclusions, for different dosage form strengths.
- comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- the source and magnitude of observed inter- and intra-subject variability for each formulation in a comparative BA study.

Appendix 1

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

Tables 1.1 and 1.2 are provided as examples of tabular formats for reporting information and results related to bioavailability and *in vitro* dissolution studies respectively. These examples give results as well as identifying the type and design of the study. Tables prepared for reporting the results of BE studies could also include the mean ratios (test/reference) for Cmax and AUC and their 90% confidence interval, or the currently recommended metrics for BE assessments.

These tables are not intended to be templates, but only to illustrate the type of information that should be considered by an applicant in designing the tables for biopharmaceutic studies. Applicants should also decide whether information and results from these studies are best

presented in tables, text or figures in order to aid clarity. If, for example, results are best presented in text and figures, tables might be used simply to list the studies.

2. SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.1 Background and Overview

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human pharmacokinetics (PK), and pharmacodynamics (PD), and *in vitro* studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarised in Items 1, 3 and 4 of Section C can also be referenced to provide a comprehensive view of the approach and rationale for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human biomaterial database. This section should not include detailed information about individual studies.

This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug-drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterise PK and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects and patients. Critical aspects of study design and data analysis should be noted, e.g., the choice of the single or multiple doses used, the study population, the choice of PD endpoints, and whether a traditional approach or a population approach was used to collect and analyse data to assess PK or PD.

2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided (see Appendix 2), together with a narrative description of the relevant features and outcomes of each of the critical individual studies that provided *in vitro* or *in vivo* data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References or electronic links to the full report of each study should be included in the narratives.

Summaries of dose-response or concentration response (PK/PD) studies with pharmacodynamic endpoints should generally be included in this section. In some cases, however, when well-controlled dose-response PD or PK/PD studies provide important evidence of efficacy or safety, they should be placed in Item 3 or 4 as appropriate and referenced, but not summarised, here.

2.3 Comparison and Analyses of Results across Studies

This section should use the results of all *in vitro* human biomaterial studies and PK, PD and PK/PD studies to characterise the PK, PD and PK/PD relationships of the drug. Results related to the inter- and intra-individual variability in these data affecting these pharmacokinetic relationships should be discussed.

This section (typically with the use of text and tables) should provide a factual presentation of all data across studies pertinent to the following:

- *in vitro* drug metabolism and *in vitro* drug-drug interaction studies and their clinical implications.
- human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualisation in the target patient population and in special populations, e.g., pediatric or geriatric patients, or patients with renal or hepatic impairment.
- comparison between single and repeated-dose PK
- population PK analyses, such as results based on sparse sampling across studies that address inter-individual variations in the PK or PD of the active drug substances.
- dose-response or concentration-response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labelling should be discussed in Item 3.4.
- major inconsistencies in the human biomaterial, PK, or PD database.

2.4 Special Studies

This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarised here. Any observed or potential effects on PK, PD, safety and/or efficacy should be considered in other appropriate sections of the Clinical Summary as well, with cross-referencing to this section. Human studies that address a specific safety issue should not be reported here, but instead should be reported in Item 4, Summary of Clinical Safety.

Example 1: Immunogenicity

For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarised in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data should be described in the efficacy section. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarised; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre (titer), timing of onset and duration of antibody responses should be summarised for each type of antibody assay used (e.g., IgG by ELISA,

neutralisation). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarised. For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analysed and summarised.

It is particularly important to summarise analyses of potential clinically relevant correlates of immunogenicity, e.g., to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events. Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug.

Example 2: Clinical microbiology

For antimicrobial or antiviral medicinal products, *in vitro* studies to characterise the spectrum of activity are an important part of the programme of studies relevant to clinical efficacy. Clinical efficacy studies that include characterisation of the susceptibility of the clinical isolates as a part of the efficacy determination should be included in Item 3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of *in vitro* susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

Appendix 2

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

Table 2.1 is provided as an example of a tabular format for reporting information and results related to pharmacokinetic drug-drug interaction studies. Similar tables could be prepared for PK/PD studies, dose-response studies, studies of effects on human biomaterials, and population PK studies. This table is not intended to be a template, but only to illustrate the type of information that should be considered by sponsors in designing their own tables. Applicants should also decide whether information and results from clinical pharmacology studies are best presented in tables, text or figures in order to aid clarity. If, for example, results are best presented in text and figures, the tables might simply list the studies.

In designing tables, if any, for various types of other clinical pharmacology studies such as those listed below, applicants should consider including the following types of information. These examples are for illustrative purposes only and the sponsor should decide which information needs to be presented.

- metabolism studies using human biomaterials: biomaterials used (e.g., microsomes, hepatocytes), probe drugs, enzymatic pathways and % contribution and relevant kinetic parameters (e.g., Vmax, Km).
- *in vitro* studies of drug-drug interactions using human biomaterials: for studies of other drugs inhibiting the new drug, the metabolite(s) inhibited, enzymatic pathways affected, range of inhibitor concentrations used, IC_{50} and K_i values and proposed mechanism of inhibition should be included. For studies of the new drug inhibiting other drugs, the

drugs and metabolites inhibited should be included, along with the information mentioned above.

- population PK studies: co-variates studied, number and type of subjects or patients studied, summary statistical parameters and final estimates of mean (± standard deviation) PK parameters.

3. SUMMARY OF CLINICAL EFFICACY

There might be time when a product may be effective for more than one indication, then a separate Section 3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 3 is submitted, the sections should be labelled 3A, 3B, 3C, etc.

3.1 Background and Overview of Clinical Efficacy

This section should describe the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought. Any results of these studies that are pertinent to evaluation of safety should be discussed in Item 4, Summary of Clinical Safety.

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of study design should be discussed, e.g., randomisation, blinding, choices of control treatment, choice of patient population, unusual design features such as crossover or randomised withdrawal designs, use of run-in periods, other methods of "enrichment", study endpoints, study duration, and prespecified plans for analysis of the study results. Although this section is intended to focus on clinical investigations, nonclinical data and clinical pharmacology data may also be referenced as appropriate to provide a comprehensive summary of human experience related to efficacy. This section should not include detailed information about individual studies.

3.2 Summary of Results of Individual Studies

A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided (see Appendix 3), together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. For studies that also contributed significantly to the safety analysis, study narratives should include information about the extent of exposure of study subjects to the test drug or control agent, and how safety data were collected. These narratives can be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

3.3 Comparison and Analyses of Results across Studies

Using text, figures, and tables as appropriate (see Appendix 3), the Item of 3.3 should summarise all available data that characterise the efficacy of the drug. This summary should

include analyses of all data, irrespective of their support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilise two kinds of analyses: comparison of results of individual studies, and analysis of data combined from various studies. Details of analyses that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Clinical Study Reports.

This section should also cross-reference important evidence from Item 2, such as data that support the dosage and administration section of the labelling. These data include dosage and dose interval recommended, evidence pertinent to individualisation of dosage and need for modifications of dosage for specific subgroups (e.g., pediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships.

3.3.1 Study Populations

The demographic and other baseline characteristics of patients across all efficacy studies should be described. The following should be included:

- the characteristics of the disease (e.g., severity, duration) and prior treatment in the study subjects, and study inclusion/exclusion criteria
- differences in baseline characteristics of the study populations in different studies or groups of studies.
- any differences between populations included in critical efficacy analyses and the overall patient population that would be expected to receive the drug when it is marketed should be noted.
- assessment of the number of patients who dropped out of the studies, time of withdrawal (a defined study day or visit during treatment or follow up period), and reasons for discontinuation.

Tabular presentations that combine and compare study populations across studies may be useful.

3.3.2Comparison of Efficacy Results of all Studies

The results from all studies designed to evaluate the drug's efficacy should be summarised and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, control group, study duration, statistical methods, patient population, and dose should be identified.

Comparisons of results across studies should focus on pre-specified primary endpoints. However, when the primary endpoints involved different variables or time points in different efficacy studies, it may be useful to provide cross-study comparisons of important data elements that were obtained in all studies. If results over time are important, results of studies may be displayed in a figure that illustrates the change over time in each study.

Confidence intervals for treatment effects should be given to aid in the interpretation of point estimates. If differences are shown between placebo and test drugs in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo and active controls (if used), should generally be presented in the table or in text

accompanying a figure. If the objective of an active control trial was to show equivalence or non-inferiority, the difference or the ratio of outcomes between treatments should be given with the confidence interval.

The results should be evaluated by using the predefined criteria for defining equivalence or non-inferiority and the rationale for the criteria and support for the determination that the study (studies) had assay sensitivity should be provided (see ICH E10).

Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross-study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (See ICH E9). A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (Clinical Study Reports).

3.3.3 Comparison of Results in Sub-populations

The results of individual studies or overview analyses of efficacy in specific populations should be summarised in this section. The purpose of these comparisons should be to show whether the claimed treatment effects are observed consistently across all relevant sub-populations, especially those where there are special reasons for concern. The comparisons may highlight apparent variations in efficacy that require further investigation and discussion. The limitations of such analyses, however, should be recognised (ICH E9), and it is important to note that their purpose is not to provide the basis for specific claims, nor to attempt to improve the evidence of efficacy in situations where the overall results are disappointing.

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) on efficacy.

Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the pediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive, detailed efficacy analyses are performed, they can be placed in Clinical Study Reports, with the results of those analyses reported here.

3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose-response or blood level-response relationships of effectiveness (including dose-blood level relationships), and thus have contributed to dose selection and choice of dose interval. Relevant data from nonclinical studies may be referenced, and relevant data from pharmacokinetic studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarised to illustrate these dose-response or blood

level-response relationships. For pharmacokinetic and pharmacodynamic studies from which data have been summarised in Item 2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in Item 2.2, without repeating those summaries.

While the interpretation of how these data support specific dosing recommendations should be supplied in the Clinical Overview document, the individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualisation of dosage) should be summarised here. Any identified deviations from relatively simple dose-response or blood-level response relationships due to non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be described.

Any evidence of differences in dose-response relationships that result from a patient's age, sex, race, disease, or other factors should be described. Any evidence of different pharmacokinetic or pharmacodynamic responses should also be discussed, or discussions in Item 2 can be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the test drug).

3.5 Persistence of Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarised. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted. Examination of any apparent relationships between dose changes over time and long-term efficacy may be useful.

The primary focus should be on controlled studies specifically designed to collect long-term efficacy data, and such studies should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see Item 4).

In long-term efficacy trials, the effect of premature discontinuation of therapy or switching to other therapies upon the assessment of the results should be considered. These issues might also be important for short term trials and should be addressed when discussing the results of these trials, if appropriate.

Appendix 3

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section.

Tables should identify all studies pertinent to the evaluation of efficacy (including studies that were terminated or are not yet completed, studies that failed to show effectiveness for any reason, studies available only as publications, studies reported in full technical reports

(ICH E3), and studies described in abbreviated reports); and should provide the most important results of those studies. Note, however, that unplanned interim analyses on ongoing studies are generally not needed or encouraged. When more than one section 3 is provided for an application with more than one indication, usually each section should have its own appendix with tables.

Illustrative tables for an antihypertensive drug are provided, but these examples will not be relevant to every application. In general, applications will require tables and/or figures that are developed specifically for the particular drug class and the studies that were carried out.

Table 3.1 Description of Clinical Efficacy and Safety Studies

Table 3.2 Results of Efficacy Studies

4. SUMMARY OF CLINICAL SAFETY

This section should be a summary of data relevant to safety in the intendedpatient population, integrating the results of individual clinical study reportsas well as other relevant reports, e.g., the integrated analyses of safety thatare routinely submitted in some regions.

The display of safety-related data can be considered at three levels (ICHE3):

- The extent of exposure (dose, duration, number of patients, type ofpatients) should be examined to determine the degree to which safetycan be assessed from the database.
- The more common adverse events and changes in laboratory testsshould be identified and classified, and their occurrence should besummarised.
- Serious adverse events (defined in ICH E2A) and other significantadverse events (defined in ICH E3) should be identified and theiroccurrence should be summarised.These events should be examinedfor frequency over time, particularly for drugs that may be usedchronically.

The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

4.1 Exposure to the Drug

4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the nonclinical data, any relevant pharmacological class effects, and the sources of the safety data (controlled trials, open studies, etc). A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided (see Appendix 4). In addition to studies that evaluated efficacy and safety, and uncontrolled studies that generate safety information, this section includes studies that consider special safety issues. Examples would include studies to compare particular adverse event rates for two therapies, to assess safety in particular demographic subsets, to evaluate withdrawal or rebound phenomena, or to evaluate particular adverse events (e.g., sedation, sexual function, effects on driving, absence of a class adverse effect). Studies in indications for which approval is not being sought in the current application and ongoing studies would also be included here if they contribute to the safety analysis.

Narrative descriptions of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in Item 3.2 and cross-referenced here. The narratives should provide enough detail to allow the reviewer to understand the exposure of study subjects to the test drug or control agent, and how safety data were collected (including the methods used and the extent of safety monitoring of the subjects enrolled in the individual studies). If some studies are not analysed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.

4.1.2 Overall Extent of Exposure

A table (see example provided in Appendix 4) and appropriate text should be generated to summarise the overall extent of drug exposure from all phases of the clinical study development programme. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes, and durations. If a large number of different doses and/or durations of exposure were used, these can be grouped in a manner appropriate for the drug. Thus, for any dose or range of doses, duration of exposure can be summarised by the number of subjects exposed for specific periods of time, such as 1 day or less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3).

In some applications it may be important to identify diagnostic subgroups and/or groups receiving specific concomitant therapies deemed particularly relevant to safety assessment in the intended use.

The dose levels used for each subject in this presentation could be the maximum dose received by that subject, the dose with longest exposure, and/or the mean daily dose, as appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m2 basis, as appropriate. If available, drug concentration data (e.g., concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables.

It is assumed that all subjects who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

4.1.3 Demographic and Other Characteristics of StudyPopulation

A summary table should provide the reader with an overview of the demographic characteristics (Table 4.2) of the population that was exposed to the therapeutic agent during its development. Choice of age ranges used should take into account considerations discussed in ICH E7 [Studies in Support of Special Populations: Geriatrics] and ICH E11 [Clinical Investigation of Medicinal Products in the Paediatric Population]. If the relative exposure of demographic groups in the controlled trials differed from overall exposure, it may be useful to provide separate tables.

In addition, one or more tables should show the relevant characteristics of the study population, and the numbers of subjects with special characteristics. Such characteristics could include:

− Severity of disease
− Hospitalisation
− Impaired renal function
− Concomitant illnesses
− Concomitant use of particular medications
− Geographical location

If these characteristics are distributed differently in controlled trials versus the overall database, it will generally be useful to present tables on both groupings.

The text accompanying the table(s) should mention any imbalance(s) between the drug and placebo and/or comparator regarding any of the above demographic characteristics, particularly if they could lead to differences in safety outcomes.

If certain subjects were excluded from studies (concomitant illness, severity of illness, concomitant medications), this fact should be noted.

Separate demographic tables should be provided for every indication, although closely related indications can be considered together, if study subject characteristics are such that risks are believed to be the same.

4.2 Adverse Events

4.2.1 Analysis of Adverse Events

Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate Item 4.2.1 and the tables that are not embedded in the text should be placed in Appendix 4.

All adverse events occurring or worsening after treatment has begun ("treatment emergent signs and symptoms," those adverse events not seen at baseline and those that worsened even if present at baseline) should be summarised in tables listing each event, the number of subjects in whom the event occurred and the frequency of occurrence in subjects treated with the drug under investigation, with comparator drugs, and with placebo. Such tables could also present results for each dose and could be modified to show, e.g., adverse event rates by severity, by time from onset of therapy, or by assessment of causality.

When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping the studies and pooling the results to improve precision ofestimates and sensitivity to differences should generally be considered.

While often useful, pooling of safety data across studies should be approached with caution because in some cases interpretation can be difficult, and it can obscure

realdifferences. In cases where differences are apparent, it is more appropriate to present the data by study. The following issues should be considered:

- it is most appropriate to combine data from studies that are of similar design, e.g., similar in dose, duration, methods of determining adverse events, and population.
- if the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- any study with an unusual adverse event pattern should be presented separately.
- the appropriate extent of analysis depends on the seriousness of the adverse event and the strength of evidence of drug causation. Differences in rates of drugrelated,serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.
- examination of which subjects experience extreme laboratory value abnormalities ("outliers") may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

Groups of studies that could be used in pooled safety analyses include:

- all controlled studies or subsets of controlled studies, such as all placebo- controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out
- in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- all studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- all studies using a particular dose route or regimen, or aparticular concomitant therapy.
- studies in which adverse event reports are elicited bychecklist or direct questioning, or studies in which eventsare volunteered.
- pools of studies by region.

It is almost always useful to carry out the first two groupings;the others chosen would vary from drug to drug and should beinfluenced by inspection of individual study results. Whatevermethods are used, it should be recognised that, as for resultsof single studies, any numerical rate is often only a roughapproximation of reality.

When a decision is made to pool data from several studies,the rationale for selecting the method used for pooling shouldbe described. It is common to combine the numerator eventsand the denominators for the selected studies. Other methodsfor pooling results across studies are available, e.g., weightingdata from studies on the basis of study size or inversely to theirvariance.

If substantial differences are seen between clinical trials in therates of adverse events, these differences should be notedand possible reasons should be discussed (e.g., relevantdifferences in study populations, in dose administration, or inmethods of collecting adverse event data).

Adverse events should be described as shown in the individualstudy report (ICH E3). In combining data from many studies,it is important to use standardised terms to describe eventsand collect synonymous terms under a single preferred term.

This can be done with international standard dictionary andterminology should be used and specified. Frequencies shouldbe presented for preferred terms and for appropriately definedgroupings. Examination of which adverse events led to changein therapy (discontinuation of drug use, change in dose,need for added therapy) can help in assessing the clinicalimportance of adverse events. These rates can be added tothe adverse event rate tables, or can be presented in separatetables. Overall discontinuation rates by study may be usefulbut it is also important to specify the particular adverse eventsleading to discontinuation in a separate table. The preferredterms should be grouped by body system and arranged bydecreasing frequency.

4.2.1.1 Common Adverse Events

Tabular displays of adverse event rates (see Appendix 4) shouldbe used to compare rates in treatment and control groups. Forthis analysis it may be helpful to combine the event severitycategories and the causality categories, if they are used,leading to a simpler side-by-side comparison of treatmentgroups. It should be noted that while causality categoriesmay be reported, if used, the presentation of the data shouldinclude total adverse events (whether deemed related orunrelated to treatment); evaluations of causality are inherentlysubjective and may exclude unexpected adverse events thatare in fact treatment related. Additionally, comparisons of ratesof adverse events between treatment and control groups inindividual trials should be summarised here. It is often usefulto tabulate rates in selected trials (see example table 4.4, inAppendix 4).

It is usually useful to examine more closely the more commonadverse events that seem to be drug related (e.g., those thatshow that a dose response and/or a clear difference betweendrug and placebo rates) for relationship to relevant factors,including:

- dosage;
- mg/kg or mg/m2 dose;
- dose regimen;
- duration of treatment;
- total dose;
- demographic characteristics such as age, sex, race;
- concomitant medication use;
- other baseline features such as renal status;
- efficacy outcomes;
- drug concentration, where available.

It may also be useful to summarise the results of examinationof time of onset and duration for these drug-related events.Rigorous statistical evaluations of the possible relationshipof specific adverse events to each of the above factors areoften unnecessary. It may be apparent from initial display andinspection of the data that there is no evidence of a significantrelationship to demographic or other baseline features. In thatcase, no further analysis of these particular factors is needed.

Further, it is not necessary that all such analyses be presentedin this report. When the safety analyses are too extensive tobe presented in detail in this report, they may be presented ina separate report in Clinical Study Reports, and summarisedhere.

Under certain circumstances, life table or similar analyses maybe more informative than reporting of crude adverse eventrates.

4.2.1.2 Deaths

A table in Appendix 4 should list all deaths occurring while on study (including deaths that occurred shortly following treatment termination, e.g., within 30 days or as specified in the study protocol, as well as all other deaths that occurred later but may have resulted from a process that began during studies). Only deaths that are clearly disease-related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in studies where mortality from disease is a primary study endpoint, should be excepted from this listing (it is assumed, however, that these deaths would still be reported in the individual ICH E3 study reports). Even these deaths should be examined for any unexpected patterns between study arms, and further analysed if unexplained differences are observed. Deaths should be examined individually and analysed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause- specific deaths. Potential relationships to the factors listed in Item 4.2.1.1 should also be considered. Although cause-specific mortality can be difficult to determine, some deaths are relatively easy to interpret. Thus deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not considered to be informative, but even one death due to a QT interval prolongationassociated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.

4.2.1.3 Other Serious Adverse Events

Summaries of all serious adverse events (other thandeath but including the serious adverse events temporallyassociated with or preceding the deaths) should be displayed.Serious adverse events that occurred after the drug use wasdiscontinued should be included in this section. The displayshould include major laboratory abnormalities, abnormal vitalsigns, and abnormal physical observations that are consideredserious adverse events using the ICH E2A definitions. Resultsof analyses or assessments of serious adverse events acrossstudies should be presented. Serious events should beexamined for frequency over time, particularly for drugs thatmay be used chronically. Potential relationships to the factorslisted in Item 4.2.1.1 should also be considered.

4.2.1.4 Other Significant Adverse Events

Marked haematologic and other laboratory abnormalities(other than those meeting the definition of serious) and anyevents that led to a substantial intervention (prematurediscontinuation of study drug, dose reduction, or substantialadditional

concomitant therapy), other than those reported asserious adverse events, should be displayed.

Events that led to premature discontinuation of study drugrepresent an important safety concern and deserve particularattention in the analysis of drug safety for two reasons. First,even for expected events (based on pharmacologic activity),the need to discontinue (or otherwise alter) treatment reflectsthe severity and perceived importance of the event to patientand physician. Second, discontinuation may represent a drugrelatedevent not yet recognised as drug related. Adverse eventsleading to treatment discontinuation should be consideredpossibly drug-related even if this was not recognised initiallyand even if the event was thought to represent intercurrentillness. Reasons for premature treatment discontinuationsshould be discussed and rates of discontinuations shouldbe compared across studies and compared with those forplacebo and/or active control treatment. In addition, the studydata should be examined for any potential relationships to thefactors listed in Item 4.2.1.1.

4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Assessment of the causality of, and risk factors for, deaths, other serious events, and other significant events is often complicated by the fact that they are uncommon. As a result, consideration of related events as a group, including less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. For example, the relationship to treatment of an isolated sudden death may become much clearer when considered in thecontext of cases of syncope, palpitations, and asymptomatic arrhythmias.

It is thus generally useful to summarise adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities.

Such presentations of adverse events by organ system shouldbe placed in Item 4.2.1.5, labelled as 4.2.1.5.1, 4.2.1.5.2, etc.,and titled by the organ system under onsideration. The list oforgan systems to be addressed and the approach to groupingcertain events should be selected as appropriate to best presentthe adverse event data for the medicinal product. If someadverse events tend to occur in syndromes (e.g., influenzalikesyndrome, cytokine release syndrome), the sponsor maychoose to create some Item 4.2.1.5 for syndromes rather thanorgan systems.

The same data and summarisations should generally not berepeated in more than one subsection of Item 4.2.1. Instead,a summary presentation may be placed in one subsection andcross-referenced as needed in the other.

4.2.2 Narratives

The locations in the application of individual narratives of patientdeaths, other serious adverse events, and other significantadverse events deemed to be of special interest because ofclinical importance (as described in ICH E3 individual studyreports) should be referenced here for the convenience of thereviewer. The narratives themselves should be a part of theindividual study reports, if there is such a report. In cases wherethere is no individual study report (e.g., if many open studiesare pooled as part

of a safety analysis and are not individuallydescribed), narratives can be placed in Clinical Study Reports,Item 5.3. Narratives should not be included here, unless anabbreviated narrative of particular events is considered criticalto the summary assessment of the drug.

4.3 Clinical Laboratory Evaluations

This section should describe changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in Item 4.2.1.3 or 4.2.1.4. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The appropriate evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis (ICH E3). Where possible, laboratory values should be provided instandard international units.

A brief overview of the major changes in laboratory values across the clinical studies should be provided. Laboratory data should include haematology, clinical chemistry, urinalysis and other data as appropriate. Each parameter at each time over the course of the study (e.g., at each visit) should be described at the following three levels:

- the central tendency, i.e., the group mean and median values,
- the range of values, and the number of subjects with abnormal values or with abnormal values of a certain size (e.g. twice the upper limit of normal, 5 times the upper limit; choices should be explained). When data are pooled from centers with differences in normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual subject changes by treatment group can be shown with a variety of approaches (e.g., shift tables, see ICH E3 for examples).
- individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g., by analysis of such features as relationship to dose, relation to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy). Potential relationships to other factors listed in Item 4.2.1.1 should also be considered.

4.4 Vital Signs, Physical Findings, and Other Observations Relatedto Safety

The manner of presenting cross-study observations and comparisonsof vital signs (e.g., heart rate, blood pressure, temperature, respiratoryrate), weight and other data (e.g., electrocardiograms, X-rays) relatedto safety should be similar to that for laboratory variables. If there isevidence of a drug effect, any dose-response or drug concentrationresponserelationship or relationship to individual variables (e.g.,disease, demographics, concomitant therapy) should be identified andthe clinical relevance of the observation described. Particular attentionshould be given to changes not evaluated as efficacy variables and tothose considered to be adverse events. Particular attention should begiven to studies that were designed to evaluate specific safety issues,e.g., studies of QT interval prolongation.

4.5 Safety in Special Groups and Situations

4.5.1 Patient Groups

This section should summarise safety data pertinent to individualising therapy or patient management on the basis of demographic, age, sex, height, weight, lean body mass, genetic polymorphism, body composition, other illness and organ dysfunction. Safety in the pediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Analysis of the impact on safety outcomes should have been presented in other sections but should be summarised here, together with pertinent PK or other information, e.g., in patients with renal or hepatic disease, the medical environment, use of other drugs (see 4.5.2, Drug Interactions), use of tobacco, use of alcohol, and food habits. For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by post-marketing experience, or by information on similar drugs, information should be provided here. If a sufficiently large number of subjects with a given co-morbid condition suchas hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to assess whether the comorbid condition affected the safety of the drug under study.

Cross reference should be made to the tables or description of adverse events when analyses of such sub-groups has been carried out.

4.5.2 Drug Interactions

Studies on potential drug-drug or drug-food interactions should be summarised in the Summary of Clinical Pharmacology Studies section of the ACTD. The potential impact on safety of such interactions should be summarised here, based on PK, PD, or clinical observations. Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.

4.5.3 Use in Pregnancy and Lactation

Any information on safety of use during pregnancy or breastfeeding that becomes available during clinical development or from other sources should be summarised here.

4.5.4 Overdose

All available clinical information relevant to overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarised and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.

4.5.5 Drug Abuse

Any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in humans should be summarised and rossreferenced to the nonclinical summary. Particularly susceptible patient populations should be identified.

4.5.6 Withdrawal and Rebound

Any information or study results pertinent to rebound effects should be summarised. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound.

Data concerning tolerance should be summarised under Item 3.5 in the Summary of Clinical Efficacy.

4.5.7 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Safety data related to any impairment in the senses, coordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarised. This includes relevant adverse effects reported in safety monitoring (e.g., drowsiness) and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.

4.6 Post-marketing Data

If the drug has already been marketed, all relevant post-marketing data available to the applicant (published and unpublished, including periodic safety update reports if available) should be summarised. The periodic safety update reports can be included in Clinical Study Reports. Details of the number of subjects estimated to have been exposed should be provided and categorised, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided. A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions. Any post-marketing findings in subgroups should be described.

Appendix 4

Tabular presentations should be provided that summarise the important results from all studies pertinent to the evaluation of safety and particularly to support product labelling. Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

A few illustrative tables are provided, but a clinical summary will routinely need tables and figures that have been developed for the particular drug, drug class, and clinical indication(s).

See Items 4.2.1, 4.2.2.3, and 4.3 of this guidance for additional discussion regarding the content of section 4 tables.

Table 4.1 Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure

Table 4.2 Demographic Profile of Patients in Controlled Trials

Table 4.3 Incidence of Adverse Events in Pooled Placebo and Active Controlled Trials

Table 4.4 Incidence of Adverse Events in the Largest Trials

Table 4.5 Patient Withdrawals by Study: Controlled Trials

Table 4.6 Listing of Deaths

5. SYNOPSES OF INDIVIDUAL STUDIES

The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of a study synopsis with each clinical study report, and provides one example of a format for such synopses.

This section should include the table entitled Listing of Clinical Studies, described in guidance for Clinical Study Reports, followed by all individual study synopses organised in the same sequence as the study reports in Clinical Study Reports.

It is expected that one synopsis will be prepared per study for use in all regions, and that the same synopsis will be included in this section and as part of the clinical study report . The length of a synopsis will usually be up to 3 pages, but a synopsis for a more complex and important study may be longer, e.g. 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

Table 1.1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No.(M/F) type Age: mean (range)	Mean Parameters (+/- SD)						Study Report Location
					Cmax (mg/L)	Tmax (hr)	AUC* (mg/Lxhr)	Cmin** (mg/L)	T1/2 (hr)	Other	
192 (Japan)	Pilot relative BA study comparing the absorption from a 200mg tablet batch to a 200mg reference batch.	Open, randomized, cross-over, single 200 mg dose	200mg Tab., p.o. [17762] 200mg Tab.. p.o. [19426]	20 (10/10) Healthy volunteer 27 y (20-35)	83 ± 21 80 ± 32	1 0.5	217 ± 20 223 ± 19		3.1 2.9		
195 (Japan)	Comparative BA study of xx under fasted and fed conditions	Open, randomized, cross-over, single dose	200mg Tab, p.o. [19426]	30 (15/15) Healthy volunteer 32 y (26-50)	83 ± 21 120 ± 30	1 2	217 ± 20 350 ± 40				

AUC*: AUC_{TAU} or AUC_{inf}

Cmin**: For multiple dose studies

Table 1.2. Summary of *In vitro* Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection times Mean % Dissolved (range)	Study Report Location
1821	979-03	25mg Cap.	Dissolution: Apparatus 2 (USP) Speed of Rotation: 50 rpm Medium/Temperature: Water 37◦	12	10 20 30 (min) 42 (32-49) 71 (58-85) 99 (96-100) (%)	

Table 2.1 Summary of Drug-Drug Interaction PK Studies

Study/ Protocol # (Country)	Product ID/Batch # (NME)	Study Objective	Study Design	# Subjects Entered/ Completed (M/F)	HV/P[1] (Age: Mean, range)	Treatments		Mean Pharmacokinetic Parameters (%CV) Substrate Drug					Mean ratio[2] Confidence interval		Location
						Substrate	Interacting Drug	Cmax	Tmax	AUC	T1/2	CL/kg	Cmax	AUC	
001 (USA)	19B Batch 0034	Effect of warfarin on Drug X	Randomized, Cross over	(8M/4F)/ (7M/4F)	HV (34, 20-41)	Drug X 100 mg bid x 7d	Placebo	45 (18) Φg/mL	2.0 (30) hr	456 (24) Φg*hr/ mL	4.25 (30) hr	0.05 (20) mL/min/kg	1.16 1.01-1.30	1.16 1.03-1.34	
						Drug X 100 mg bid x 7d	Warfarin 10 mg qd x 7d	52 (20) Φg/mL	2.1 (35) hr	530 (27) Φg*hr/ mL	4.75 (35) hr	0.04 (22) mL/min/kg			
001 (USA)	19B Batch 0034	Effect of drug X on warfarin	Randomized, Cross over	(8M/4F)/ (7M/4F)	HV (34, 20-41)	Warfarin 10 mg qd x 7d	Placebo	12 (25) Φg/mL	1.5 (30) hr	60 (37) Φg*hr/ mL	40 (35) hr	0.04 (30) mL/min/kg	1.08 0.92-1.24	1.07 0.92-1.18	
						Warfarin 10 mg qd x 7d	Drug X 100 mg bid x 7d	13 (20) Φg/mL	1.45 (27) hr	64 (39) Φg*hr/ mL	42 (37) hr	0.39 (34) mL/min/kg			
002 (UK)	19B2 Batch 0035	Effect of Cimetidine on Drug X	Cross over, Single sequence	(4M/8F) (4M/8F)	HV (30, 19-45)	Drug X 50 mg bid x 5d	Placebo	49 (18) Φ/mL	2.1 (30) hr	470 (24) Φg*hr/ mL	4.4 (30) hr	0.05 (20) mL/min/kg	1.22 1.03-1.40	1.36 1.11-1.53	
						Drug X 50 mg bid x 5d	Cimetidine 200 mg bid x 5d	60 (10) Φg/mL	2.2 (30) hr	640 (24) Φg*hr/ mL	5.2 (30) hr	0.03 (20) mL/min/kg			

[1]HV=Healthy Volunteers, P=Patients

[2]Value for substrate with interacting drug / value with placebo

Table 3.1 Description of Clinical Efficacy and Safety Studies

Study ID	Number of Study Centers Location(s)	Study start Enrollment status, date Total enrollment / Enrollment goal	Design Control type	Study & Ctrl Drugs Dose,Route & Regimen	Study Objective	# subjs by arm Entered/ compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
PG-2476	1 U. Antarctica	Aug-94 Completed Apr 98 50 / 50	Randomised, double blind, parallel Placebo	TP: 30 mg po bid Pbo	Efficacy and Safety	27/24 23/21	4 weeks	27/23 38 (20-64)	Mild hypertension Diastolic 90-100 Systolic 150-170	Change from baseline systolic and diastolic pressure at 4 weeks.
PG-2666	4 Affiliated Physicians of Florida, 126/400 Smith & Jones CRO	May-98 Ongoing as of May 2001	Randomised, open label, parallel Placebo and Dose-response	TP: 100 mg po bid TP: 50 mg po bid TP: 25 mg po bid Placebo	Efficacy and Safety, Long-term efficacy and safety	34/30 30/28 34/32 28/26	4 weeks, followed by 12 weeks open-label	66/60 55 (24-68)	Mild hypertension Systolic 150-170 Diastolic 90-100	Change from baseline systolic and diastolic pressure at 4 weeks and at 12 weeks.

Table 3.2 Results of Efficacy Studies

Study	Treatment Arm	# Enrolled/Completed	Mean systolic and diastolic BP			Primary Endpoint	Statistical test / P value	Secondary Endpoints	Other Comments
			Baseline	20 wks	40 wks	Placebo-subtracted change in DBP at 40 weeks		% normalised** (ITT analysis)	
PG-2678	TP: 100 mg po bid	34/30	162/96	140/85	138/84	6		88	
	TP: 50 mg po bid	30/28	165/97	146/87	146/87	4		78	
	TP: 25 mg po bid	34/32	167/96	148/88	148/88	2		50	
	TP: 10 mg po bid	26/20	162/95	153/93	153/93	-4		20	
	Placebo	28/26	166/97	160/92	159/91			30	

**Provide definition

Table 4.1 Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure Intravenous formulation **N=** **Cutoff Date:**								
Duration **(Weeks)**	**Mean Daily Dose (mg)**							
	0 < Dose ≤ 5mg	5 < Dose ≤ 10mg	10 < Dose ≤ 20mg	20 < Dose ≤ 30mg	30 < Dose ≤ 50mg	50mg < Dose	Total (Any Dose)	Percent
0 < Dur ≤ 1								
1 < Dur ≤ 2								
2 < Dur ≤ 4								
4 < Dur ≤ 12								
12 < Dur ≤ 24								
24 < Dur ≤ 48								
48 < Dur ≤ 96								
Dur >96								
Total (Any Duration)								
Percent								

Similar tables can be generated for median, for modal, and for maximum dose, or for dose of longest exposure. The same table can be generated for any pool of studies and any subgroup of interest, e.g., on the basis of age groupings, sex, ethnic factors, comorbid conditions, concomitant medications, or any combination of these factors.

Dose can also be expressed as mg/kg, mg/m^2, or in terms of plasma concentration if such data are available.

Table 4.2 Demographic Profile of Patients in Controlled Trials Cutoff Date:			
	Treatment Groups		
	Test Product N =	Placebo N =	Active Control N =
Age (years)			
Mean ± SD	50 ± 15		
Range	20-85		
Groups			
<18			
18 - 40	N (%)	N (%)	N (%)
40 - 64	N (%)	N (%)	N (%)
65 - 75	N (%)	N (%)	N (%)
>75	N (%)	N (%)	N (%)
	N (%)	N (%)	N (%)
Sex			
Female	N (%)	N (%)	N (%)
Male	N (%)	N (%)	N (%)
Race			
Asian	N (%)	N (%)	N (%)
Black	N (%)	N (%)	N (%)
Caucasian	N (%)	N (%)	N (%)
Other	N (%)	N (%)	N (%)
Other Factors			

Table 4.3 Incidence of Adverse Events in Pooled Placebo and Active Controlled Trial Database

Body System / Adverse Event	Test Drug			**Placebo**	**Active Control 1**	**Active Control 2**	
	All doses n = 1685	**10 mg n = 968**	**20 mg n = 717**	**n = 425**	**20 mg n = 653**	**50 mg n = 334**	**100 mg n = 546**
Body as a whole							
Dizziness	19 (1%)	7 (1%)	12 (2%)	6 (1%)	23 (4%)	1 (<1%)	3 (1%)
Etc.							
Cardiovascular							
Postural Hypotension	15 (1%)	10 (1%)	5 (1%)	2 (<1%)	7 (1%)	6 (2%)	12 (2%)
Etc.							
Gastrointestinal							
Constipation							

Table 4.4 Incidence of Adverse Events in Individual Studies								
	Reported incidence by Treatment Groups							
Body System / Adverse Event	Study 95-0403			**Study 96-0011**		**Study 97-0007**		**Study 98-0102s**
	Drug x 60 mg bid N =104	**Drug x 30 mg bid N =102**	**Placebo N = 100**	**Drug x 60 mg bid N = 500**	**Placebo N=495**	**Drug x 60 mg bid N=200**	**Drug y 100 mg qd N=200**	**Drug x 60 mg bid N=800**
Body as a whole								
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular								
Postural Hypotension								
Etc.								
Gastrointestinal								
Constipation								

Table 4.5 Patient Withdrawals[1] by Study: Controlled Trials **Cutoff Date:**									
Studies		*Total Withdrawal*				*Reason for Withdrawal*			**Number without post-withdrawal efficacy data**
		Total	**Male/ Female**	**Age > 65**	**Race (identify groupings) / / /**	Adverse Events N (%)	Lack of Efficacy N (%)	Other N (%)	N (%)
Study	Drug X	*N (%)*	*N (%) / N (%)*	*N (%)*	*N (%) / N (%) / N (%)*				
XXX	Placebo								
Study	Drug X								
AAA	Comparator A								
Study	Drug X								
BBB	Comparator B								
Study	Drug X								
CCC	Comparator C								
All Trials									

Note: withdrawal data can be subdivided by dose level, if that appears to be useful.

[1] Withdrawals are all subjects who were enrolled but did not complete the planned course of treatment (includes subjects who discontinued treatment or changed to a different treatment prematurely and/or were lost to follow-up)

Table 4.6 Listing of Deaths

Treatment: Test Product **Cutoff Date:**

Trial / Source[1]	Center	Patient ID	Age (yrs)	Sex	Dose (mg)	Duration of exposure (Days)	Diagnosis	Cause of Death	Other medications	Other medical conditions	Location of narrative description

[1]PM = deaths from postmarketing experience

This listing should include all deaths meeting the inclusion rule, whether arising from a clinical trial or from any secondary source, e.g., postmarking experience. In electronic applications, a link to the narrative or other documentation regarding the event should be provided.

A footnote should describe the rule for including deaths in the table, e.g., all deaths that occurred during a period of drug exposure or within a period of up to 30 days following discontinuation from drug and also those occurring later but resulting from adverse events that had an onset during exposure or during the 30 day follow up period. Other rules may be equally appropriate.

Similar lists should be provided for patients exposed to placebo and active control drugs.

D. TABULAR LISTING OF ALL CLINICAL STUDIES

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in E: Clinical Study Reports

Table 1. Listing of Clinical Studies

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	20	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	Cross-over	Two tablet formulations, 50 mg, oral	32	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	Cross-over	Tablet, 50mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	24 (12 drug, 12 placebo)	Patients with primary hypertension	2 weeks	Ongoing; Interim

Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full

SECTION E: CLINICAL STUDY REPORTS

PREAMBLE

For ASEAN member countries, the Study Reports of this part may not be required for NCE, biologics, vaccines, and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who requires specific Study Reports should ask for the necessary documents. The ICH E3 provides guidance on the organisation of clinical study reports, other clinical data, and references within the ASEAN Common Technical Dossier (ACTD) for registration of a pharmaceutical product for human use. In this case, the applicant will submit Section A, B, C. D and F.

Guideline on Organisation of Clinical Study Reports and Related Information

This guideline recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections.

An explanation such as “not applicable” or “no study conducted” should be provided when no report or information is available for a section or subsection.

A. TABLE OF CONTENTS FOR STUDY REPORTS

A Table of Contents for the study reports should be provided.

B. TABULAR LISTING OF ALL CLINICAL STUDIES

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section C below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

C. CLINICAL STUDY REPORTS

1. Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal and biologics, however BA studies is not required for vaccine. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Item 3.1, and referenced in Items 1.1 and/or 1.2.

1.1 Bioavailability (BA) Study Reports

BA studies in this section should include 1) studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability

of the drug substance given intravenously or as an oral liquid dosage form 2) dosage form proportionality studies, and 3) food-effect studies.

1.2 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between 1) the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, 2) the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and 3) similar drug products from different manufacturers.

1.3 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in Item 1.3.

Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the ACTD.

1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Item 1.4 and referenced in the appropriate individual study reports.

2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used *in vitro* or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways.

Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Part III).

2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies should be provided in Item 3.

2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

2.3 Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in this section.

3. Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity.

The PK studies whose reports should be included in Item 3.1 and 3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or feces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells.

On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Item 3.1 to 3.2, as appropriate. These studies should characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Item 3.1 and/or 3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability.

Pharmacokinetic studies are usually not applicable for vaccines. However, such studies (Healthy Subject PK and Initial Tolerability Study) might be

applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients. In this occasion, these studies should be included in this section.

3.1 Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this

section.

3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

3.3 Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials

including efficacy and safety trials, should be placed in this section.

4. Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Item 5.

This section should include reports of 1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers), 2) short-term studies of the main clinical effect, and 3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects should be placed in Item 4.1, and the reports for those studies conducted in patients should be placed in Item 4.2.

In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Item 5, not in Item 4.

In relation to vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterise the immune response to the vaccine. Therefore, this section will focus on considerations for an appropriate range of immunogenicity studies that may be conducted throughout the clinical development programme. The applicant should justify the final range of tests performed, with an explanation of the rationale for each investigation, in the Clinical Overview.

4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be

placed in this section

4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

5. Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and non-proposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and individual guidance by region).

Within Item 5, studies should be organised by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Item 5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate Item 5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Item 5 and referenced as necessary in other Items 5, e.g., Item 5A, Item 5B.

5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in Item 5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Item 5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Item 5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in Item 5.1.

Particularly for vaccine, control clinical studies are conducted in phase II or phase III studies. These control studies can include placebo control, dose or schedule – response control, active comparators, lot control (to assess lot consistency), population or age group control, etc.

Phase I studies are intended to define the safety and reactogenicity of the vaccine and to seek preliminary information on immunogenicity. Design of phase I studies are usually-open label studies and are not randomized with placebo control groups.

Phase II vaccine trials are intended to demonstrate the immunogenicity of the relevant active component(s) and the safety profile of a candidate vaccine in the target population.

Ultimately, the phase II studies should define the optimal dose, initial schedule and safety profile of a candidate vaccine before the phase III trials can begin.

The phase III studies are large-scale clinical trials designed to provide data on vaccine efficacy and safety. These studies are usually performed in large populations to evaluate efficacy, immunogenicity and safety of formulation(s) of the immunologically active component(s). In largescale efficacy studies of this type, that may enroll many thousands of subjects, serological data are usually collected from at least a subset of the immunized population at pre-defined intervals.

Clinical lot-to-lot consistency trials are conducted to provide an assessment of manufacturing consistency in addition to the information provided on the manufacturing process. Clinical lot-to-lot consistency trials might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients.

5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included. This includes studies in conditions that are not the subject of the marketing application.

5.3 Reports of Analyses of Data from More than One Study

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Item 5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications.

For case of combined vaccines or vaccines made by new manufacturers, information on bridging studies should be submitted to ensure the non-inferiority of the vaccine under evaluation compared with the reference vaccine, supporting immunogenicity, reactogenicity, safety, and efficacy, when applicable.

5.4 Other Clinical Study Reports

This section can include:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports of clinical experiences with the medicinal product that are not included in Item 5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Item 5.1
- Reports of ongoing studies

ACTD Check List for Product Classification
(ASEAN Common Technical Dossier on Clinical Data for Pharmaceutical Registration)

Part IV : Clinical Document	NCE	BIOLOGICS	MaV			MiV	GP	VACCINE				
			RT	ST/P	IND			NV	NC	NV-EA	IND	S/P
Section A. Table of Contents	✓	✓	✓	✓	✓	-	-	✓	✓	✓	✓	✓
Section B. Clinical Overview	✓	✓	✓	✓	✓	-	-					
1. Product Development Rationale								✓	✓	✓	✓	✓
2. Overview of Biopharmaceutics								-	-	-	-	-
3. Overview of Clinical Pharmacology								*	*	-	*	-
4. Overview of Efficacy								✓	✓	✓	✓	✓
5. Overview of Safety								✓	✓	✓	✓	✓
6. Benefits and Risks Conclusions								✓	✓	✓	✓	✓

Part IV : Clinical Document	NCE	BIOLOGICS	MaV			MiV	GP	VACCINE				
			RT	ST/P	IND			NV	NC	NV-EA	IND	S/P
Section C. Clinical Summary	✓	✓	✓	✓	✓	-	-					
Summary of Biopharmaceutic Studies and Associated Analytical Method 1.1 Background and Overview 1.2 Summary of Results of Individual Studies 1.3 Comparison and Analyses of Results Across Studies Appendix 1								-	-	-	-	-
Section C. Clinical Summary (Cont.) **Summary of Clinical Pharmacology Studies** 2.1 Background and Overview 2.2 Summary of Results of Individual Studies 2.3 Comparison and Analyses of Results Across Studies 2.4 Special Studies Appendix 2								* *	* *	- 	* *	-

Part IV : Clinical Document	NCE	BIOLOGICS	MaV			MiV	GP	VACCINE				
			RT	ST/P	IND			NV	NC	NV-EA	IND	S/P
Summary of Clinical Efficacy 3.1 Background and Overview of Clinical Efficacy 3.2 Summary of Results of Individual Studies 3.3 Comparison and Analyses of Results Across Studies 3.4 Analysis of Clinical Information Relevant to Dosing Recommendations 3.5 Persistence of Efficacy and/or Tolerance Effects Appendix 3								✓	✓	✓	✓	✓

Part IV : Clinical Document	NCE	BIOLOGICS	MaV			MiV	GP	VACCINE				
			RT	ST/P	IND			NV	NC	NV-EA	IND	S/P
Section C. Clinical Summary (Cont.) **Summary of Clinical Safety** 4.1 Exposure to the Drug 4.2 Adverse Events 4.3 Clinical Laboratory Evaluations 4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety 4.5 Safety in Special Groups and Situations 4.6 Post-marketing Data Appendix 4								✓	✓	✓	✓	✓
Synopses of Individual Studies								✓	✓	✓	✓	✓
Section D. Tabular Listing of All Clinical Studies	✓	✓	✓	✓	✓	-	-	✓	✓	✓	✓	✓

NCE - New chemical entity
RT - New Route of Administration
S/P - New Strength and Posology
IND - New Indication
NC - New Combination
NV - New/Novel Vaccine, including new adjuvanted vaccine
CV/EV - Conventional Vaccine / Established Vaccine
✓ - Required
- - Not Required
❖ - Where applicable, i.e. change of route of administration due to change in formulation, change of formulation and posology such as immediate release to sustained released) and/or for product with narrow margin of safety or variable kinetics
♦ - Generally inappropriate for Biological products, however, product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (e.g. Growth factors, immunosuppressive agents, etc.)
*) - Repeated toxicity study may not be needed if no difference in formulation compared to the approved vaccine. Different manufacturer may have different formulation, process and/or composition although the antigen have been established. Hence, the toxicity profile and tolerance may differ with the approved vaccine
- Where Applicable (Note: Vaccine efficacy data is generally required, unless otherwise scientifically justified.)

Notes:
1. As references for requirement, the following WHO Guidelines or their relevant updates are used:
   a. Guidelines on procedures and data requirements for changes to approved vaccines (WHO TRS 993, Annex 4)
   b. Guidelines on procedures and data requirements for changes to approved biotherapeutic products (2017)
   c. WHO Guidelines on nonclinical evaluation of vaccines (WHO TRS 927, Annex 1)
   d. Guidelines on clinical evaluation of vaccines: regulatory expectations (WHO TRS 1004, Annex 9)
   e. Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (WHO TRS 987, Annex 2)
2. The term ‘Biologics’ used in this document does not include vaccines with the rationale that vaccines has different characteristics compared with other biological products so that in many cases the requirements are different.