**Johnson & Johnson Pharmaceutical Research & Development**

# Guideline for the Preparation of Clinical Expert Reports

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Medical Writing
Global Clinical Operations

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## BACKGROUND AND SUPPORTING DOCUMENTATION

The following is a guideline in the preparation of the content and format of the Clinical Expert Report (CER). This guideline is based primarily on the following guidance document:

- Notice to Applicants for Marketing Authorisations for Proprietary Medicinal Products for Human Use in the Member States of the European Community; Volume II of The Rules Governing Medicinal Products in the European Community, 1998 (heretofore referred to as Notice to Applicants).

Other regulatory sources for this guideline include the following:

- Directive 75/319/EEC

This guideline also refers to the following:

- Johnson & Johnson Pharmaceutical Research and Development (J&JPRD) Guideline for the Preparation of Clinical Study Reports (in preparation);
- Janssen Research Foundation (JRF)/The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) Style Guidelines for Clinical Documents (May, 2001)
- Training and Reference Documentation for Clinical GRIPS (Global Research and Information Publishing System) Users (September 1999), a reference manual that described specific procedures involved in creating, authoring, modifying and approving the documents in GRIPS.
- J&JPRD-GCO-SOP 701 on the process to "Prepare Information for Clinical Expert Report/Clinical Overview" (in preparation).

## OVERVIEW

**Directive 75/319/EEC** as amended requires that the particulars and documents submitted in the application dossier are drawn up and signed by experts, with the necessary technical or professional qualifications. The Clinical Expert Report is 1 of 3 Expert Reports included in the dossier, the other 2 being the Pharmaceutical Expert Report and the Pharmaco-toxicological Expert Report. All 3 Expert Reports, their tabular formats, and written summaries are placed in Part IC of the dossier. The standard format for the application is given in Guideline Attachment 1.

It is important to emphasize that well-prepared Expert Reports greatly facilitate the task of the competent authority in evaluating the dossier and contribute towards the speedy processing of applications. For these reasons particular care should be taken in the preparation of Expert Reports, following the guidance on the preparation of Expert Reports given in the current edition of the Notice to Applicants. In the Clinical

Expert Report, the Clinical Expert is expected to take and defend a clear position on the product in the light of current scientific knowledge.

The Clinical Expert Report must contain a critical evaluation of the methodology, results and conclusions of studies presented in the dossier, rather than a numerical recitation of the data. The critical analysis should be dispersed throughout the document and may require additional analyses beyond those presented in the individual summaries or integrated analyses to address specific issued raised by the European experts or health authorities. As the length of the Clinical Expert Report text (Introduction through Conclusions) **should not exceed 25 pages**, this review of the dossier must be concise without sacrificing clarity.

A sample format of the dossier Part IC that includes the Clinical Expert Report is contained in Guideline Attachment 2. The "critical assessment" portion of the Clinical Expert Report is preceded by a Product Profile and followed by information on the qualifications of the Clinical Expert (based on his or her curriculum vitae), tabular study summaries/synopses, and a written (factual) summary.

## Purpose

The purpose of this guideline is to provide uniform standards for the format and content of the Clinical Expert Report. This guideline is intended to assure consistency in the quality and format of the Clinical Expert Report across therapeutic areas within J&JPRD. J&JPRD-GCO Standard Operating Procedure (SOP) 701 and related training materials provide a detailed map of the process of preparing the Clinical Expert Report in its entirety starting from an intention to file starting point, through developing key messages, selecting and briefing the Clinical Expert, and drafting and finalizing the published report in GRIPS.

## Scope of Guideline

This guideline should be used for the preparation of Clinical Expert Reports that provide information relevant to the efficacy and safety of the drug and are intended for J&JPRD regulatory submission in support of any such safety or efficacy claims. In general, the Clinical Expert Report is part of a dossier to be submitted in Europe covering EEC (European Economic Community) countries as well as EFTA (European Free Trade Association) countries, but is not limited to these countries.

***CAVEAT***: It is recognized that beginning July 2003, the use of the Common Technical Document (CTD) format will become mandatory. Therefore although the window of use for this guideline on the Clinical Expert Report may be limited, some

countries may still require submission of a "traditional" Clinical Expert Report in addition to accepting a filing using CTD format.

## General Considerations

**Conformance to Notice to Applicants**

While this document presents general guidelines, as suggested by the Notice to Applicants, the format can be adapted as necessary for an individual marketing authorization by expanding or contracting sections, adding sections and omitting sections where not relevant. The use of graphs and tables is encouraged to facilitate understanding of the data.

**Scope of the Expert Report**

As a general rule, there should be 1 Clinical Expert Report written for each drug indication. Thus, information relevant to the different clinical trials in which the drug may be administered at different strengths, by different routes, or in various patient populations, can be complied into a single cohesive summary. In some cases, however, multiple reports may be written to accommodate the various medical specialities as they pertain to various parts of the indication.

**Report Annotation**

The Clinical Expert Report and the summaries of data should contain precise volume and page cross-references to the specific study reports or other relevant information, such as the literature, indicating where that information is found in the dossier. It is recommended that these references (annotations) be typed in the right margin of the text and in a separate column or at the top of tables. In addition, copies of articles or abstracts referenced in the Clinical Expert Report should be included in the dossier. Final annotation cannot be completed until the dossier has been fully paginated.

## REPORT ORGANIZATION AND CONTENT DETAILS

The following presents details regarding the content of each report section consistent with the organization of the J&JPRD Clinical Expert Report template. Discussion of these elements is based on both the Notice to Applicants and the company experience in preparing Clinical Expert Reports. For further elaboration of these items, see the Notice to Applicants, as well as particulars for Clinical Expert Reports for Abridged Applications.

## Title Page/Signature Page

The title page contains both the title of the report and the signature of the Clinical Expert who signs the report. It should include the following components:

- Report type – "Expert Report on the Clinical Documentation" and title. The report title should generally match the sought indication.
- Name and affiliation of the Clinical Expert, his or her signature, and the date signed. Affiliation refers to the Expert's division or department where he or she conducts work, and address (street address, city, state/province, zip code and country).

The signature page must be included in the copy of the dossier sent to the various regulatory agencies where Clinical Expert Reports are required. While it is highly recommended to have 1 "signing" Clinical Expert, there is to be 1 signature page for each expert who contributed to the report in cases of multiple experts. The Clinical Expert Report can be signed by either an external Clinical Expert or an internal signatory. In either case the company retains primary responsibility for the dossier including the Expert Reports.

A sample title/signature page from the Clinical Expert Report template is shown in Guideline Attachment 3.

## Table of Contents

A Table of Contents is not specified in the Notice to Applicants, but should be included. It should be comprehensive and clear to allow the reviewer easy access to information. The Table of Contents authored in-house using the virtual document (VD) template should be generated electronically in GRIPS using the publishing software application. In addition to the general guidelines, specific requirements are as follows:

- The Table of Contents should be prepared for the main body of the Clinical Expert Report including Appendices and can include up to 5 outline levels with the corresponding page numbers. It is not general practice to include a separate List of Tables and Figures as these are generally limited within the report main body. The page numbers in the paper document should be identical to those in its Portable Document Format (PDF) version. The report Title/signature page is not numbered and is followed by Page 2 starting with the Table of Contents page. The pagination continues sequentially throughout the rest of the document.

The Table of Contents as presented in the Clinical Expert Report template is contained in Guideline Attachment 4.

## Product Profile

Each Expert Report should be introduced by a "product profile" (1 to 2 pages), which is a brief extract of the Summary of Product Characteristics (SmPC) and which repeats the key points listed below. This product profile, as an extract of the SmPC, does not have to be signed by the expert.

- **Type of Application**
  - a product essentially similar to 1 already on the market, or
  - a new active substance(s), or
  - a new combination of previously known active substance(s), or
  - a new pharmaceutical form, or
  - a new strength, or
  - an extension of indications.
- **Chemical and Pharmacokinetic Properties**
  - the chemical structure of the active substance(s);
  - the physicochemical properties of the active substance(s) and the characteristics of the pharmaceutical form that could have an effect on the pharmacokinetic parameters and clinical efficacy.
- **Indications**
  - the therapeutic indications proposed as a function of the posology and their justification;
  - the pharmacological and therapeutic classification of the active substance(s), defining the mode of action.
- **Precautions**
  - significant precautions and warnings derived from the principal results of the preclinical studies, both toxicology and animal pharmacology.
- **Marketing/Postmarketing**
  - a list of any postmarketing surveillance;
  - a list of marketing authorizations already issued in other countries, and those applied for.

The Product Profile taken from the Clinical Expert Report template is shown in Guideline Attachment 5.

## Main Body of Expert Report ("Critical Review")

An outline of the main body of the Clinical Expert Report ("critical review") is given in Table 1; the template for these sections is presented in Guideline Attachment 6. This guideline presents relevant details on the contents of each section. The numbered headings in this guideline correspond to the heading numbering in the template.

**Table 1**: Outline of the Main Body ("Critical Review") Portion of the Clinical Expert Report

| | |
|---|---|
| Section **1.** | Introduction and Problem Statement |
| Section **2.** | Clinical Pharmacology |
| Section **3.** | Clinical Trials |
| Section **4.** | Postmarketing Experience |
| Section **5.** | Other Information |
| Section **6.** | Conclusions |

## 1. INTRODUCTION AND PROBLEM STATEMENT

The Introduction presents information on the background of the disease or condition studied and the current therapy (if applicable) citing any unmet medical need. A brief overview of the investigational product is given focusing on its pharmacologic action and mechanism, relevant pharmacokinetic or pharmacodynamic properties, and any relevant preclinical data from animal studies. Reference may be made to other indications for marketing authorization that the medicinal product may have received.

The Problem Statement should be concise and centered upon clinical practice with reference to the contribution that the investigational drug could make in light of the current therapeutic indication claimed and any potential advantages over existing therapies. The rationale for the drug development program is given briefly as well as any Regulatory guidelines used to develop the trial protocols. While not required, the Problem Statement may contain a summary of conclusions reached from analysis of the data.

# 2. CLINICAL PHARMACOLOGY

## 2.1. Overview

The Overview includes a brief discussion of the scope and type of studies from which pharmacodynamic and pharmacokinetic data are drawn including key conclusions supporting the drug's intended use.

## 2.2. Pharmacokinetics

### 2.2.1. Pharmacokinetics of the Active Substance(s)

The report should provide the pharmacokinetic profile and parameters, dealing with the active substance(s) and as appropriate with active metabolite(s).

- *Present results in relation to population studied:*
  - healthy volunteers;
  - subjects for intended therapeutic indication (particularly with respect to the blood/plasma concentrations achieved at steady state during the study);
  - subjects at increased risk, for physiological reasons (e.g., children or elderly), or for additional pathologic reasons, such as renal failure or liver insufficiency.
- *Include results for the following pharmacokinetic parameters:*
  - absorption rate and extent, and if appropriate the influence of food;
  - distribution including binding with plasma proteins and the distribution volumes;
  - metabolism, including results concerning possible genetic polymorphism, and the formation of active and inactive metabolites;
  - excretion of the unchanged substance or metabolites;
  - parameters relevant to the rate and route of elimination should be assessed (elimination half-life, partial and total clearances).

The discussion of results should highlight clinically significant features such as: 1) the range of inter/intra-individual variations, 2) non-linearity, 3) diffusion into the fluids and target tissues for the indication, 4) accumulation, 5) role of metabolites in the clinical effect, and 6) liver enzyme induction. In addition, the implication of the pharmacokinetic data for the dosage regimen under normal conditions of use and in high-risk subjects, the possible interactions between the excipients of a fixed

combination, and differences between human and the animal data should be discussed.

### 2.2.2. Bioavailability/Bioequivalence and Absorption

The pharmacokinetic results ($C_{max}$, $t_{max}$, AUC) relevant to the comparison of formulations used in clinical development and particularly those proposed for marketing, should be assessed. Data interpretation should take into account results of dissolution rate studies.

Systemic absorption from pharmaceutical forms intended to have a non-systemic effect should be summarized and presented as described above using results with blood/plasma, urine or feces levels. The clinical significance of systemic absorption, with respect to possible adverse effects, should be discussed.

### 2.2.3. Drug-Drug Interactions

Possible pharmacokinetic interactions between the substance and other medicinal products or substances that are likely to be taken simultaneously should be described and discussed in terms of clinical relevance. Consideration should be given to results of the observations made in clinical pharmacologic studies as well as clinical trials.

## 2.3. Pharmacodynamics

- *All important pharmacodynamic data should be presented including the following:*
  - characteristics of the population studied (e.g., healthy volunteers, subjects under investigation for current indication or other indication with explanation why pharmacodynamic data can be extrapolated from 1 population to another);
  - description and validation of the experimental methods and their relevance;
  - clinical and laboratory results as a function of dose or concentration that are pertinent to the therapeutic efficacy and safety.
- *Pharmacodynamic data should indicate the following:*
  - the pharmacodynamic action correlated to the therapeutic effect, including the dose-response relationship (intensity and duration);
  - the optimal dose and conditions of administration;
  - the mode of action;

- any pharmacodynamic actions not correlated with the therapeutic effect;
- the actions on different organs or physiological functions;
- any unwanted effects seen as a function of dose, as well as those that might have been anticipated on the basis of the demonstrated pharmacodynamic properties.

If no specific pharmacodynamic studies were conducted, the pharmacodynamic effects of the drug, as a primary or secondary efficacy or safety parameter, may be discussed in the Clinical Trials section (Section 3).

## 2.4. Pharmacokinetic/Pharmacodynamic Relationships

Drug concentration information, if available, should be analyzed in pharmacokinetic terms and related to the response. Any apparent relationship between response and concomitant therapies and past or concurrent illnesses should be described.

# 3. CLINICAL TRIALS

## 3.1. Overview of Clinical Program and Quality

The purpose of this section is to provide a brief overview of the clinical development program including the total number of trials by type, with cross-reference to Appendix A for more detailed information, and an Overall Tabular display of studies (inserted as "new" Appendix C) if prepared for complex applications. Any European regulatory guidances on the evaluation of the medicinal product (or class of product) in review used in trial design should be cited, noting their absence and alternative guidance used if applicable. The logical chronologic progression of the clinical program should be briefly stated particularly if early trials failed to adequately demonstrate either efficacy or safety and if information is gained over time regarding proper dosing in the intended treatment population.

Comments regarding the conduct of the trial in accordance with the Declaration of Helsinki and its amendments, national requirements, and on conformity with the principles of Good Clinical Practices (GCP) should be made. In addition, statements may be included regarding the standards used to conduct the trial and their analysis (i.e., "state-of-the-art" procedures) and conduction of any internal study audits may be made.

## 3.2. Efficacy in Clinical Trials

The summary of results and the critical evaluation in this section should give a clear picture of the therapeutic efficacy. The most important and significant studies should be summarized individually. When discussing these studies the Clinical Expert should give special emphasis to the assessment of trials that give unequivocal evidence of the efficacy (Phase 2 or 3 studies) and provide a justification for the dosage regimens.

### 3.2.1. Statistical Methodology in Efficacy Studies

This section should contain a high-level description of those methods of analysis that provide the basis for making statistical inferences. The planned primary endpoint(s) (if applicable) for studies providing unequivocal efficacy results should be stated. In addition, a description of any plans for interim analyses of efficacy data should be given if applicable, noting any possible consequences, i.e., termination or change in study design.

### 3.2.2. Individual Study Results

The section should include a concise discussion of each relevant study that includes: the protocol objective and design, subject selection criteria, study population characteristics (comparability of groups), type and duration of treatment, criteria for evaluation of efficacy, the number of subjects contributing efficacy data and any excluded, and any significant protocol violations/deviations. The results of each parameter of efficacy should be presented as a function of dose administered, with a statistical evaluation. Primary efficacy variables should be presented before secondary variables and in greater detail. Unless conflicting results are obtained using alternative analyses or different subpopulations, results should be presented for the preferred method of analysis and primary subpopulation only. The possibility of bias should be discussed and a judgment should be made on the clinical significance of the results. Where appropriate, factors influencing response to therapy, such as baseline or demographic characteristics, concomitant illness or therapy, or other covariates or prognostic factors, should be discussed.

### 3.2.3. Integrated Analysis [if Applicable]

This section should include an examination of study-to-study differences in results, effects in subsets of the treated population, and dose-response information across studies individually or when considering a pooled population of studies of similar design. If certain subgroups that are

candidates for treatment with the study drug have not been included (e.g., older subjects or those with hepatic or renal impairment), so that the effectiveness of the study drug has not been assessed in them, this should be noted and the implications considered.

### 3.2.4. Overall Assessment of Efficacy

Conclusions with respect to efficacy results should be concisely described, indicating the number of trials showing a positive and negative result, accompanied with appropriate explanations. A tabular summary of key efficacy results across the studies is often the most concise presentation. The relationship between efficacy and dosage regimen should be justified and defined for each indication (if multiple indications), in the different subgroups of subjects, with mention of the percentages of successes and failures. For medicinal products intended for long-term use, maintenance of long-term efficacy and the establishment of long-term dosage should especially be discussed.

If the treatment could be improved through plasma concentration monitoring, documentation for an optimal therapeutic plasma range should be included.

The therapeutic efficacy of the tested medicinal product should be assessed by comparison with other reference therapies. For fixed combinations, the therapeutic value should equally be considered by comparison to each of the individual components used separately. The doses and proportions of the components should be justified. A full account of the therapeutic advantages of such an association should be given.

## 3.3. Safety in Clinical Trials

The primary emphasis in this section should be on a critical review of treatment-emergent adverse events and clinical laboratory results (if applicable), which should be summarized appropriately with statistical evaluation, where relevant. Other information pertinent to the safety of the study drug should also be discussed.

### 3.3.1. Adverse Events

A full assessment should be made of adverse events including those related to abnormal laboratory values. The total subject population studied must be defined. The number of subjects for which there is adequate documentation to enable an assessment of safety should be stated.

Adverse events should be grouped by body system and preferred term. A clinical judgment should be made on the relationship to treatment, the frequency and the seriousness of the observed adverse events. The overall figures should be analyzed appropriately in subgroups according to pertinent factors such as age, sex, race, diagnosis, dosage used, etc. The nature and frequency of dose reduction should be indicated addressing any clinically important implications. This section should include poisoning reactions (overdose), the potential for dependence, and rebound phenomena, if known.

Subjects with a particular risk factor should be highlighted. The numbers of subjects treated for specific durations of time, graded from short-term to, where relevant, long-term, should be indicated, i.e., number of subjects treated for at least 1 year.

The incidence of death, other serious adverse events, and other significant adverse events (including discontinuation due to adverse events) should be discussed.

### 3.3.2. Clinical Laboratory Tests [if Applicable]

Clinical laboratory results should be summarized with statistical evaluations, where relevant. Note any clinically important patterns or trends including markedly abnormal laboratory measurements.

### 3.3.3. Overall Assessment of Safety

A critical assessment of the overall safety profile of the study drug should take into account the adverse reactions recorded in light of the disease treated, the study drug studied relative to other applicable therapies, subgroup subject characteristics, and preclinical data on toxicology and pharmacology. Special attention should be paid to any unusual or unexpected findings that could represent previously unsuspected adverse events and subject groups at risk identified, as appropriate. The major toxicities associated with the study drug's use should be clearly stated and a medical opinion rendered with regard to causality, subject management under the conditions of use, and monitoring. Recommendations should be made for the conditions of study drug use that may include modifications of dosage regimens, monitoring of blood/plasma levels, contraindications, warnings, and precautions for use.

# 4. POSTMARKETING EXPERIENCE

If the product is already on the market in some countries, reported adverse reactions should be given, in relation to the usage rates in those countries. The discussion should also include the methods of detection and assessment of those adverse reactions. The results should clearly show how the postmarketing data complement or modify the safety profile and the conditions for use. One may include whether postmarketing studies are planned and the nature of those studies.

**NOTE**: The writing of the postmarketing experience should be a collaborative effort between the report author and the Drug Safety and Surveillance (DSS) department. The DSS department is responsible for maintaining the postmarketing experience database regarding the study drug that includes reports received by the company from postmarketing studies, spontaneous reports, as well as cases from the literature. Thus, DSS is well suited to render a medical opinion relative to the above.

# 5. OTHER INFORMATION

This section contains information not covered in the other parts of the report. Studies discontinued prematurely should be mentioned and reasons given. While the Notice to Applicants suggests a description of ongoing studies, giving their nature, size, objectives, and projected completion dates with results, judgment should be exercised on the need to include this information as relevant to review of the dossier.

# 6. CONCLUSIONS

This section should cover the following points with critical data cited as needed to highlight key findings.

## 6.1. Therapeutic Justification

The therapeutic justification should focus on what contribution the study drug could make towards meeting current unmet medical needs in the targeted patient population (as presented in the Problem Statement in Section 1), and advantages over existing therapies. This justification is especially relevant for fixed combination products and new pharmaceutical forms.

## 6.2. Efficacy

The discussion should clearly present the key efficacy data that justify the proposed indication with mention of supporting efficacy results. New data should not be introduced, nor should all the results be reiterated. Any relationship between parameters and the significance of any conflicting results within or between relevant studies should be noted and explained.

## 6.3. Safety

This section should briefly assess the overall safety profile of the study drug based on adverse events, clinical laboratory findings, other safety observations, and also consider any relevant preclinical pharmacology and toxicology. Adverse events, contra-indications, clinically significant interactions (and possible recommendations for use that would be appropriate), warnings and precautions should be defined. Treatment of overdosage should be described. The possible utilization during pregnancy and breast-feeding and the possible effect on driving ability should be taken into account.

## 6.4. Proposed Dosage Regimen

The proposed dosage regimen should be stated in terms of dose range (starting dose or range, titration, maximum daily dose), dosing considerations regarding the age or sex of the subject or organ dysfunction (e.g., renal or hepatic impairment), and duration of treatment.

## 6.5. Risk/Benefit Assessment

The risk/benefit ratio for the product should be judged with regard to clinical practice and the different treatments that are available.

# Remaining Report Sections

# 7. REFERENCES

In general, references cited should include, but are not limited to, the most current clinical data on the disease/conditions studied. Articles appearing in refereed journals, proceedings, or books are preferred citations over other types of literature having undergone generally less rigorous review.

All references to published or unpublished literature cited in the Clinical Expert Report should be listed. References should be cited in accordance with the JRF/RWJPRI Style Guidelines for Clinical Documents. References

should be numbered and each reference annotated to its location within the application file.

The template reference section is included in Guideline Attachment 7.

## 8. INFORMATION ON THE CLINICAL EXPERT

Attached to the report, there should be brief (1 page) information on the expert(s): their name(s), educational background, training and occupation. The professional relationship of the expert to the applicant should be declared. The qualifications and experience of the expert should be briefly summarized, either descriptively or through inclusion of the Expert's curriculum vitae. Although only 1 expert may assume responsibility for the report, other experts may contribute to its preparation, according to their expertise.

The Information on the Clinical Expert section of the template is presented in Guideline Attachment 8.

## 9. APPENDICES

The tabular formats included as Appendix A and B accompanying the Expert Report, in accordance to those set out in the Notice to Applicants, provide a standardized approach to the presentation of the documentation in tabular form. Equally, the formats are in many cases designed to facilitate the assessment, which in turn benefits the applicant.

The Summary of Clinical Documentation (Appendix C), also commonly known as the Written (or Factual) Summary should be factual, complete (i.e., covering all studies), and concise. It should contain cross-references to the documentation in the relevant part of the dossier as well as including tables, graphs, etc.

## Appendix A: Tabular Summary of Clinical Studies

A tabular presentation of all clinical trials and studies should be given. This should contain the principal characteristics of the trials, such as study and study report identifier, country in which it took place, design, number of subjects by age and sex, diagnosis and criteria for inclusion, duration of treatment, dose regimen and route of administration, criteria for evaluation, key efficacy results and adverse reactions, and the location of the study report in the dossier.

For a better understanding, it is recommended to successively present information relating to controlled trials followed by non-controlled trials.

The format of Appendix A from the template is shown in Attachment 9.1 (cover page) and Attachment 9.2 (formatted tables) of the guideline. Attachment 9.3 contains an example of a completed tabular summary.

## Appendix B: Detailed Summaries of Individual Clinical Studies

The detailed summaries of individual clinical studies are directly imported from the Synopsis section of the individual study reports (see The J&JPRD Guideline for the Preparation of Clinical Study Reports for greater detail).

A sample format of Appendix B from the template is given in Guideline Attachment 10.

## Appendix C: Summary of Clinical Documentation

The written summary has proven useful, particularly for large complex dossiers. The written summary should be factual, complete (i.e., covering all studies), and concise. Normally, it would not be longer than 30 pages. However, in cases of complex dossiers, with multiple indications or large numbers of subjects evaluable for safety and efficacy, a larger summary (up to 100 pages) could be necessary.

The Notice to Applicants does not provide an outline of the contents of Appendix C. Guideline Attachment 11.1 contains the cover page of Appendix C from the template. This is followed by a generic outline for Appendix C in Guideline Attachment 11.2 indicating the typical contents of the Summary of Clinical Documentation. Guideline Attachment 11.3 contains a sample Table of Contents for Appendix C.

## Appendix D: References in Clinical Expert Report

All references cited in the Clinical Expert Report and contained in the Reference section should be submitted. Guideline Attachment 12 presents the cover page for Appendix D from the template.

# ATTACHMENTS TO THE GUIDELINE

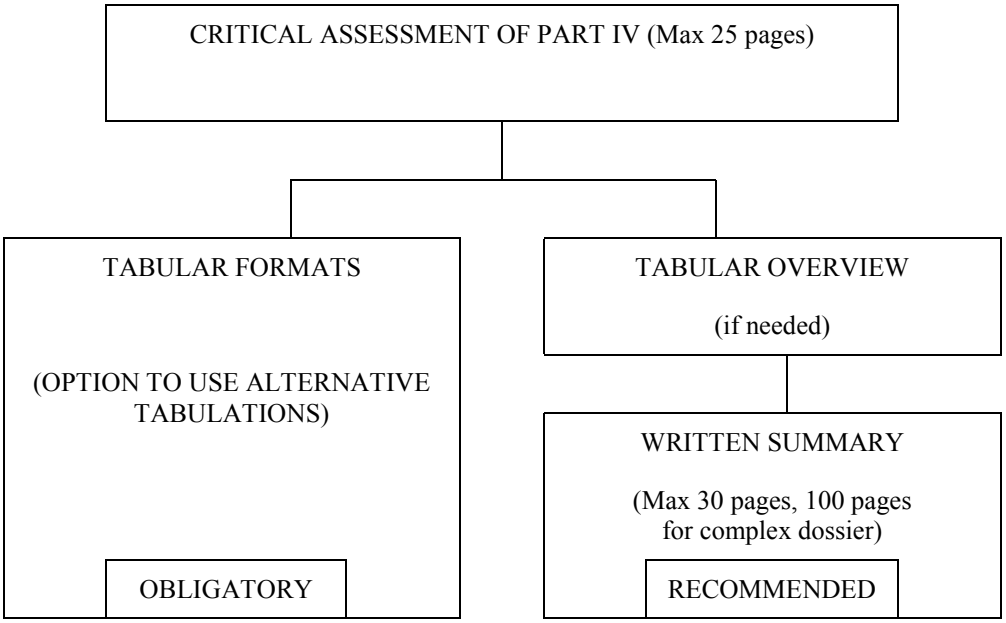
**Attachment 1:** Standard Format for Applications in the EEC
(National and Community Procedure)

**TABLE OF CONTENTS**

| | | |
|---|---|---|
| **PART I:** | IA | Administration data |
| *SUMMARY OF DOSSIER* | IB | Summary of Product Characteristics |
| | IC | Expert Reports on Chemical, Pharmaceutical and Clinical Documentation |
| **PART II:** | II | Table of Contents |
| *CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION* | IIA | Composition |
| | IIB | Method of Preparation |
| | IIC | Control of Starting Materials |
| | IID | Control Tests on Intermediate Products |
| | IIE | Control Tests on the Finished Product |
| | IIF | Stability |
| | IIQ | Other Information |
| **PART III:** | III | Table of Contents |
| *PHARMACO-TOXICOLOGICAL DOCMENTATION* | IIIA | Single Dose Toxicity |
| | IIIB | Repeated Dose Toxicity |
| | IIIC | Reproduction Studies |
| | IIID | Mutagenic Potential |
| | IIIE | Oncogenic/carcinogenic Potential |
| | IIIF | Pharmacodynamics |
| | IIIG | Pharmacokinetics |
| | IIIH | Local Tolerance (toxicity) |
| | IIIQ | Other Information |
| **PART IV:** | IV | Table of Contents |
| *CLINICAL DOCUMENTATION* | IVA | Clinical Pharmacology |
| | IVB | Clinical Experience |
| | IVQ | Other Information[a] |
| **PART V:** | V | Table of Contents |
| *SPECIAL PARTICULARS* | VA | Dosage Form |
| | VB | Samples |
| | VC | Manufacturers Authorization(s) |
| | VD | Marketing Authorization(S) |

[a] May include literature references to Expert Report

**Attachment 2:** Format of Dossier Part 1C: Expert Report



**Attachment 3:** Title Page from Template

Expert Report

On the Clinical Documentation

[Title]

Signature: _____ Date: _____

[Name, M.D.]
[Title]
[Affiliation]
[Division or Department]
[Street Address]
[City, State/Province, Zip Code]
[Country]

**Attachment 4:** Word Generated Table of Contents from Template

# TABLE OF CONTENTS

**Attachment 5:** Product Profile from Template

Part/Vol/Page

## PRODUCT PROFILE

Type of Application
[Text]

Chemical and Pharmacokinetic Properties
[Text]

[Structure graphic]

[Text]

Indications
[Text]

Precautions
[Text]

Marketing/Postmarketing
[Text]

**Attachment 6:** Main Body of Report from Template

Part/Vol/Page

## 1. INTRODUCTION AND PROBLEM STATEMENT

[insert paragraph 1]

[insert paragraph 2]

### 1.1. [Insert Heading]

### 1.2. [Insert Heading]

## 2. CLINICAL PHARMACOLOGY

### 2.1. Overview

### 2.2. Pharmacokinetics

#### 2.2.1. Pharmacokinetics of the Active Substance(s)

#### 2.2.2. Bioavailability/Bioequivalence and Absorption

#### 2.2.3. Drug-Drug Interactions

### 2.3. Pharmacodynamics

### 2.4. Pharmacokinetic/Pharmacodynamic Relationships

**Attachment 6:** Main Body of Report from Template (Continued)

Part/Vol/Page

**3. CLINICAL TRIALS**

**3.1. Overview of Clinical Program and Quality**

**3.2 Efficacy in Clinical Trials**

**3.2.1. Statistical Methodology in Efficacy Studies**

**3.2.2. Individual Study Results**

**3.2.3. Integrated Analysis [if applicable]**

**3.2.4. [Insert Heading]**

**3.2.5. Overall Assessment of Efficacy**

**3.3. Safety in Clinical Trials**

**3.3.1. Adverse Events**

**3.3.2. Clinical Laboratory Tests [if Applicable]**

**3.3.3. [Insert Heading]**

**3.3.4. Overall Assessment of Safety**

**4. POSTMARKETING EXPERIENCE**

**5. OTHER INFORMATION**

**Attachment 6:** Main Body of Report from Template (Continued)

## 6. CONCLUSIONS

### 6.1. Therapeutic Justification

### 6.2. Efficacy

### 6.3. Safety

### 6.4. Proposed Dosage Regimen

### 6.5. Risk/Benefit Assessment

**Attachment 7:** Reference Section from Template

Part/Vol/Page

## 7. REFERENCES

1. Author(s). Title. Journal Year; Volume: pages (range).
2.
3.
4.
5.
6.
7.

**Attachment 8:** Information on the Clinical Expert from Template

## 8. INFORMATION ON THE CLINICAL EXPERT

[Insert CV or descriptive text]

**Attachment 9.1:** Appendix A Cover Page from Template

**Appendix A**

Tabular Summary of Clinical Studies

**Attachment 9.2:** Appendix A Tabular Summary from Template

Appendix A1 - Summary of Placebo-Controlled Clinical Trials

| NAME OF COMPANY: Johnson & Johnson Pharmaceutical Research & Development, [L.L.C.] [a division of Janssen Pharmaceutica N.V.] [a division of Janssen-Cilag Ltd.]<br><br>NAME OF FINISHED PRODUCT:<br><br>NAME OF ACTIVE INGREDIENT(S): | | | | | | | SUMMARY OF CLINICAL TRIALS REFERRING TO PART _____ OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) | |
|---|---|---|---|---|---|---|---|---|---|
| Part<br>Volume<br>Page | Study<br>-Investigator<br>-Centre(s)<br>-Report No. | Design | No. of Subjects<br>Age<br>Sex | Diagnosis +<br>Criteria for<br>Inclusion | Duration of<br>Treatment | Dose Regimen<br>and Route of<br>Administration | Criteria for Evaluation | Efficacy Results | Adverse Reactions |

**Attachment 9.2:** Appendix A Tabular Summary from Template (continued)

Appendix A2 - Summary of Controlled Clinical Studies with Reference Therapies

| NAME OF COMPANY: Johnson & Johnson Pharmaceutical Research & Development, [L.L.C.] [a division of Janssen Pharmaceutica N.V.] [a division of Janssen-Cilag Ltd.]<br><br>NAME OF FINISHED PRODUCT:<br><br>NAME OF ACTIVE INGREDIENT(S): | SUMMARY OF CLINICAL TRIALS REFERRING TO PART _____ OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|

| Part<br>Volume<br>Page | Study<br>-Investigator<br>-Centre(s)<br>-Report No. | Design | No. of Subjects<br>Age<br>Sex | Diagnosis +<br>Criteria for<br>Inclusion | Duration of<br>Treatment | Dose Regimen and<br>Route of Administration<br>Study Drug | <br><br>Reference Therapy | Criteria for<br>Evaluation | Efficacy Results | Adverse Reactions |
|---|---|---|---|---|---|---|---|---|---|---|

**Attachment 9.2:** Appendix A Tabular Summary from Template (continued)

Appendix A3 - Summary of Non-Controlled Clinical Studies

| NAME OF COMPANY: Johnson & Johnson Pharmaceutical Research & Development, [L.L.C.] [a division of Janssen Pharmaceutica N.V.] [a division of Janssen-Cilag Ltd.]<br><br>NAME OF FINISHED PRODUCT:<br><br>NAME OF ACTIVE INGREDIENT(S): | | | | | | | SUMMARY OF CLINICAL TRIALS REFERRING TO PART _____ OF THE DOSSIER | | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|---|---|---|---|---|---|---|
| Part<br>Volume<br>Page | Study<br>-Investigator<br>-Centre(s)<br>-Report No. | Design | No. of Subjects<br>Age<br>Sex | Diagnosis +<br>Criteria for<br>Inclusion | Duration of Treatment | Dose Regimen and Route of Administration | Criteria for Evaluation | Efficacy Results | Adverse Reactions |

## **Attachment 9.3:** Appendix A Sample Tabular Summary

### **Appendix A1.1** - Tabular Summary of Clinical Trials – Pivotal Single-Dose Trials

| NAME OF COMPANY: The R.W. Johnson Pharmaceutical Research Institute<br>NAME OF FINISHED PRODUCT: TRADENAME™<br>NAME OF ACTIVE INGREDIENT(S): tramadol hydrochloride + paracetamol | SUMMARY OF CLINICAL TRIALS REFERRING TO PART IV OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|

| Part Volume Page | Study Protocol -Investigator -Country -Report No. | Design | No. of Subjects Age Range Sex (M/F) | Diagnosis + Criteria for Inclusion | Duration of Trt. | Dosage Regimen and Route of Administration | Criteria for Evaluation | Efficacy Results | Adverse Reactions |
|---|---|---|---|---|---|---|---|---|---|
| | TRAMAP-ANAG-010<br>-T. Kiersch<br>-US<br>-EDMS-USRA-5029378 | Phase 3, randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in dental pain. | 400<br>16-46<br>151/249 | Moderate or severe pain as result of oral surgical procedure involving extraction of two or more impacted third molars, two of which required bone removal. | Single dose | Oral treatment with 75 mg TRAM/ 650 mg PARA; 75 mg TRAM; 650 mg PARA; 400 mg IBU; or PL. | Efficacy: SPID, SPRID, TOTPAR, time to remed., overall assessment of therapy, time to onset of perceptible and meaningful pain relief.<br>Safety: AEs | All active treatments sign. superior to PL for TOTPAR, SPID, & SPRID over 0-8 hours. TRAM/PARA sign. superior to TRAM & PARA for TOTPAR, SPID, & SPRID over 0-8 hours and time to remed. TRAM/PARA sign. superior to TRAM and PL and equal to PARA for times to onset of perceptible and meaningful pain relief and overall assessment. TRAM/PARA sign. superior to IBU for time to onset of perceptible pain relief. | Higher frequency of AEs with TRAM/ PARA & TRAM primarily due to nausea and vomiting. No deaths. SAEs: 1 TRAM. D/Cs due to AEs: 3 TRAM, 2 IBU, 2 PL. |
| | TRAMAP-ANAG-012<br>-B. Tomasetti –US<br>-EDMS-USRA-5038511 | Phase 3, randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in dental pain. | 400<br>16-46<br>179/221 | Moderate or severe pain as result of oral surgical procedure involving extraction of two or more impacted third molars, two of which required bone removal. | Single dose | Oral treatment with 75 mg TRAM/ 650 mg PARA; 75 mg TRAM; 650 mg PARA; 400 mg IBU; or PL. | Efficacy: SPID, SPRID, TOTPAR, time to remed., overall assessment of therapy, time to onset of perceptible and meaningful pain relief.<br>Safety: AEs | All active treatments sign. superior to PL for TOTPAR, SPID, & SPRID over 0-8 hours. TRAM/PARA sign. superior to TRAM & PARA for TOTPAR, SPID, & SPRID over 0-8 hours, time to remed., and overall assessment of therapy. TRAM/PARA sign. superior to PL, IBU (meaningful pain relief excepted) & TRAM and equal to PARA for time to onset of perceptible and meaningful pain relief. | Higher frequency of AEs with TRAM/ PARA & TRAM primarily due to nausea & vomiting. No deaths, SAEs, or D/Cs due to AEs. |

KEY: No. = number; US = United States; F = female; M = male; TRAM/PARA = tramadol/paracetamol; TRAM = tramadol; PARA = paracetamol; IBU = ibuprofen; PL = placebo; Trt. = treatment; remed. = remedication; combo. = combination; AE = adverse event; SAE = serious adverse event; D/C = discontinuation; sign. = (statistically) significantly superior ($p \leq 0.05$).

**Attachment 10.1:** Appendix B Cover Page from Template

## Appendix B

Detailed Summaries of Individual Clinical Studies

Note: [To be taken from individual Clinical Study Reports]

**Attachment 10.2:** Appendix B Detailed Summary from Template

# SYNOPSIS

| | | |
|---|---|---|
| NAME OF SPONSOR/COMPANY:<br>Johnson & Johnson Pharmaceutical Research & Development, [L.L.C.] [a division of Janssen Pharmaceutica N.V.] [a division of Janssen-Cilag Ltd.]<br><br>NAME OF FINISHED PRODUCT:<br><br>NAME OF ACTIVE INGREDIENT(S): | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER<br><br>Volume:<br><br>Page: | (FOR NATIONAL AUTHORITY USE ONLY) |
| **Protocol No.:** [insert protocol number]<br>**Title of Study:** [insert title] | | |
| **[Coordinating] [Principal] Investigator:** First name Last name, M.D. - Institution/Clinic Name, City, State; Country | | |
| **Publication (Reference):** | | |
| **Study Initiation/Completion Dates:** [i.e., date of first study-related procedure/observation - date of last observation for last subject; recorded as part of the database.] | | **Phase of development:** [#] |
| **Objectives:** | | |
| **Methodology:** | | |
| **Number of Subjects (planned and analyzed):** | | |
| **Diagnosis and Main Criteria for Inclusion:** | | |
| **Test Product, Dose and Mode of Administration, Batch No.:** | | |
| **Reference Therapy, Dose and Mode of Administration, Batch No.:** | | |
| **Duration of Treatment:** | | |

**Attachment 10.2:** Appendix B Detailed Summary from Template (continued)

# SYNOPSIS (CONTINUED)

| | | |
|---|---|---|
| NAME OF SPONSOR/COMPANY:<br>Johnson & Johnson Pharmaceutical Research & Development, [L.L.C.] [a division of Janssen Pharmaceutica N.V.] [a division of Janssen-Cilag Ltd.]<br>NAME OF FINISHED PRODUCT:<br>NAME OF ACTIVE INGREDIENT(S): | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER<br>Volume:<br>Page: | (FOR NATIONAL AUTHORITY USE ONLY) |
| **Criteria for Evaluation:**<br>Pharmacokinetics: [if applicable]<br>Efficacy:<br>Safety:<br>Pharmacokinetic/Pharmacodynamic Relationships: [if applicable] | | |
| **Statistical Methods:** | | |
| **SUMMARY – CONCLUSIONS**<br>PHARMACOKINETICS: [if applicable]<br>EFFICACY RESULTS: [text & table]<br>SAFETY RESULTS: [text & table]<br>PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: [if applicable]<br>CONCLUSION:<br>Date of the report: [dd Mmmm yyyy] | | |

**Attachment 11.1**: Appendix C Cover Page from Template

**Appendix C**

Summary of Clinical Documentation

**Attachment 11.2:** Summary of Clinical Documentation: Generic Outline

**LIST OF IN-TEXT TABLES AND FIGURES**

**LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

**PART 1- EFFICACY SUMMARY**

1. **INTRODUCTION**
2. **STUDY DESIGNS AND STUDY POPULATION**
3. **STATISTICAL METHODS**
4. **INDIVIDUAL STUDY RESULTS**
5. **INTEGRATED EFFICACY RESULTS**
6. **SUMMARY AND CONCLUSION**

**PART 2 – SAFETY SUMMARY**

1. **INTRODUCTION**
2. **METHODOLOGY FOR COLLECTION, EVALUATIONS, AND ANALYSIS OF SAFETY DATA**
3. **SAFETY ASSESSMENTS**
4. **DATA SUMMARIES AND ANALYSES**
5. **SAFETY FROM COMPLETED CLINICAL STUDIES**
6. **SAFETY FROM ONGOING STUDIES**
7. **SAFETY FROM PHASE 1 STUDIES**
8. **CLINICAL LABORATORY EVALUATIONS**
9. **SUMMARY AND DISCUSSION**
10. **CONCLUSIONS**
11. **REFERENCES**

**Attachment 11.3:** Sample Summary of Clinical Documentation Table of Contents

## TABLE OF CONTENTS

**Attachment 11.3:** Sample Summary of Clinical Documentation Table of Contents (Continued)

## TABLE OF CONTENTS (CONTINUED)

**Attachment 11.3:** Sample Summary of Clinical Documentation Table of Contents (Continued)

## TABLE OF CONTENTS (CONTINUED)

**Attachment 12:** Appendix D Cover Page from Template

**Appendix D**

References in Clinical Expert Report