Volume 2B

Notice to Applicants

Medicinal products for human use

Presentation and format of the dossier

Common Technical Document (CTD)

Introduction	Edition June 2006
Module 1	Edition May 2008
Module 2	Edition July 2003
Module 3	Edition July 2004
Module 4	Edition July 2004
Module 5	Edition July 2004
Herbals	Edition July 2003

Foreword

This Notice to Applicants (NTA) has been prepared by the European Commission in consultation with the competent authorities of the Member States, the European Medicines Agency and interested parties in order to fulfil the Commission's obligations with respect to article 6 of Regulation (EC) No. 726/2004, and with respect to the Annex I to Directive 2001/83/EC as amended[1].

The first edition of the Notice to Applicants (Volume 2 in the series "The Rules governing medicinal Products in the European Union") was published in 1986. A revised and completed version, the second edition, was issued in January 1989. In 1993, the procedures for applications for marketing authorisations were amended, and the centralised and mutual recognition procedures became applicable from 1995. It was decided to separate the procedural and presentational parts of this guidance as Volumes 2A and 2B respectively. In 2000, a need for additional specific regulatory guidelines was recognised and a Volume 2C was prepared. The NTA is now published in the following volumes:

Volume 2A dealing with **procedures** for marketing authorisation

Volume 2B dealing with the **presentation and format** of the application dossier

Volume 2C dealing with **regulatory guidelines**.

The latest updates of all of the above-mentioned volumes can be found on the European Commission's pharmaceutical unit's web-site at the following address: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm.

[1] Directive 2003/63/EC, OJ L 159 27.6.2003 p.46

Introduction

Volume 2B is concerned with the **presentation of the application dossier** and was first published as a separate volume in 1998. It provides guidance for the compilation of dossiers for applications for European marketing authorisations and is applicable for the centralised procedure and national procedures, including mutual recognition and decentralised procedures. The update takes account of the international agreements on the structure and format of the **Common Technical Document (CTD)** which were agreed in November 2000 within the International Conference on Harmonisation (ICH) framework and further documents and revised guidelines agreed upon since that time. This introduction should be read together with other published documents (e.g. documents published on the ICH-website: http://www.ich.org, and "questions and answers" published on the Website of the European Commission).

The update of the NTA, Vol. 2B: EU-CTD also reflects the revised ICH CTD-guidelines (see http://www.ich.org) for Quality, Safety and Efficacy. The revised ICH-guidelines were signed off at the ICH meeting in Washington, September 02. The reasons for revision were minor changes in the numbering and the headings of the CTD, which have been incorporated in the updated Modules 2, 3, 4 and 5 of the EU CTD NTA.

Module 1 was updated in April 2006 taking into account the requirements of the new pharmaceutical legislation.

To each Module a list of relevant CHMP /ICH-guidelines is annexed, which have to be taken into consideration when preparing an EU Marketing authorisation dossier. These will be updated at regular intervals.

The CTD is an internationally agreed format for the preparation of applications to be submitted to regulatory authorities in the three ICH regions of Europe, USA and Japan. It is intended to save time and resources and to facilitate regulatory review and communication. The CTD gives no information about the content of a dossier and does not indicate which studies and data are required for a successful approval. Regional requirements may affect the content of the dossier submitted in each region, therefore the dossier will not necessarily be identical for all regions.

The CTD indicates an appropriate format for the data that have been required in an application. Applicants should not modify the overall organisation of the Common Technical Document as outlined in the guideline. However, in the Non-clinical and Clinical Summaries, applicants can modify individual formats if needed to provide the best possible tabulated presentation of the technical information, in order to facilitate the understanding and

evaluation of the results.

The new EU-CTD-presentation will be applicable for all types of marketing authorisation applications irrespective of the procedure (CP, MRP, DCP or national) and of type of application (stand alone, generics etc). The CTD-format will be applicable for all types of products (new chemical entities, radiopharmaceuticals, vaccines, herbals etc.) To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.

Terminology

The Common Technical Document was developed as an international document, and therefore specific European legal terms such as “active substance”, “medicinal product”, and “marketing authorisation” were not used in its development. Applicants are reminded that the term “medicinal product” covers both pharmaceutical and biological medicinal products. Unless otherwise indicated, it should be considered to be synonymous with the term “drug product”. Similarly, the term “active substance” should be considered as synonymous with “drug substance”.

The terms used in the ICH documents may be used in the CTD part of the application.

Presentation of European Marketing Authorisation Applications:

The current requirements for the content of the European application dossier are set out in Annex I to Directive 2001/83/EC as amended, as stated in Article 8.3 “the application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I”

Annex I of Directive 2001/83/EC sets out the legal provision for implementation of the CTD-format.

The provision of this update of Volume 2B (EU CTD), which take into account the ICH agreements, replaces the previous structure of the European marketing authorisation dossier described in the 1998 edition of Volume 2B.

From 1st July 2003, all applications should be made entirely in accordance with the EU-CTD presentation outlined in the July 2003 edition of NTA, Vol. 2B or its subsequent updates.

In order to take into account experience with CTD structure and changes of a technical or scientific nature, it is anticipated that NTA, Volume 2B will be updated regularly and

additional guidance will be provided in the form of Question & Answer [2]documents as experience is gained.

Applicants are advised to consult the Commission web-site: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm to verify the latest updated information.

Presentation of Applications in the Mutual Recognition Procedure or Decentralised Procedure:

All new applications have to be submitted in accordance with the CTD format.
For Mutual Recognition Procedure based on marketing authorisation approved to the old format it is an obligation to reformat the Quality data of the dossiers before starting a new Mutual Recognition Procedure or a Repeat use procedure after 1.5.2005. For Repeat use procedures and duplicate applications/multiple applications there is no need to reformat the non-clinical and clinical data of dossiers for medicinal products for human use, authorised before 1 July 2003. Furthers guidance is given in section "presentation of the application" and the corresponding Annex to the Question & Answer document.

If the original Part II contained data on bioequivalence, then this data should be extracted from the Part II and reformatted into the new CTD structure, and annexed in a separate binder as a separate section 5.3.1.2.

The applicants are strongly reminded and encouraged to submit the Quality part of a dossier in the EU-CTD format as soon as possible.

If a MAH wants to reformat the dossier into the CTD-format, it must first be submitted to the RMS, who has to take this reformat of the dossier into account. For updating the Assessment Report it will be sufficient for the RMS to attach one page to the Assessment Report explaining that the format of the relevant dossier has been changed to the CTD-format but not the content of the dossier.

Presentation of Follow-up Measures, Specific Obligations and PSURs

Also for the submission of Follow-up Measures, a Specific Obligation dossier or a dossier including post-marketing experience, the CTD structure needs to be used.

The CTD structure should always be utilised whereby documents are assigned to the most appropriate sections in Modules 1-5. They should be structured according to the granularity defined in the ICH guidance on CTD Organisation, Annex: Granularity Document (CHMP

[2] Question & Answer document: Presentation and content of the dossier Common Technical Document (CTD) Volume 2B. Notice to Applicants. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

/ICH/2887/99 Rev 2 Correction Organisation CTD) with Tables of Content and tab dividers for paper submissions or as separate files according to eCTD guidance.

When submitting via the Centralised Procedure the Post-authorisation Guidance provided on the EMEA website (http://www.emea.eu.int/htms/human/postguidance/list.htm) should also be followed.

The PSUR should be located in Module 5.3.6, Reports of Post-Marketing Experience. If a Summary Bridging Report is also to be provided then this should be included in Module 5.3.6 as well.

Reformatting of dossiers of already authorised products:

There is no obligation to reformat the dossier of already authorised medicinal products into the new EU-CTD format.
If a marketing authorisation holder (MAH) wishes to reformat the documentation, such reformatting will be allowed, although it is not recommended for the Non-clinical and Clinical parts of the documentation. However, for the Quality part of the documentation, companies are encouraged to voluntarily reformat into the CTD-format, especially to facilitate the handling of variations and line extensions after 1st July 2003. Such reformatting must however involve the complete Quality parts, including any Drug Master Files (if applicable) and also including and integrating all approved variations. A signed declaration from the MAH, must also be submitted stating that the content/data of the Quality Module is identical to the currently approved Quality part and that there has been no changes to the dossier as a result of the reformatting.

Re-formatted Quality documentation submitted in the CTD-format must consist of a new Module 3 in CTD format, but need not necessarily contain the Quality Overall Summary together with the signed template for the Quality Expert.

A Module 1 need not be submitted. If the original Part II contained data on bioequivalence, then this data should be extracted from the Part II and reformatted into the new CTD structure, and annexed in a separate binder.

The submission of reformatted documentation should preferably occur simultaneously but separately with the submission of a variation, extension or renewal. A clear distinction between the reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation / line extension or renewal should be made. Any reformatted documentation should also be submitted in electronic format (e-CTD) if available.
Reformatting of a dossier does not fall under the legal definition of a variation, because there is no amendment of the dossier's content. For dossiers of products which are already

approved via Mutual Recognition Procedure in more than one Member State, any reformatting has to be made simultaneously in all the Member States concerned. Where products are approved via national procedures in different Member States it is also highly recommended to reformat the dossiers at the same time.

The relevant competent authority has to decide whether a fee would be charged or not.

In case of Mutual Recognition Procedures the reformatted dossier (new CTD) format of an already approved medicinal product cannot be submitted directly to the Concerned Member States. It must first be submitted to the Reference Member State, who has to take this reformat into account. For the RMS it will be sufficient to attach one page to the Assessment Report explaining that the format has been changed and not the content.

Presentation of the application

The Common Technical Document is organized into five modules. The content of Module 1 is defined by the European Commission in consultation with the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and interested parties. Concerning the structure of Modules 2, 3, 4, and 5 they are common for all ICH regions.

Administrative, regional or national information is provided in Module 1 This module contains the specific EU-requirements for the administrative data (e.g. the application form, the proposed summary of product characteristics, labelling and package leaflet, etc.).

Module 2 contains high level summaries (the Quality Overall Summary, the Non-clinical Overview / Summaries, and the Clinical Overview / Summaries), which must be prepared by suitably qualified and experienced persons (experts). Although the term "Expert Report" must be maintained for legal reasons, the content is expected to be given in the Quality Overall Summary, the Non-clinical Overview / Summaries, and the Clinical Overview / Summaries documents. Old Expert Reports are now replaced by Module 2. The experts have to sign and add brief information on their educational background and specific expertise in a special section in Module 1.4.

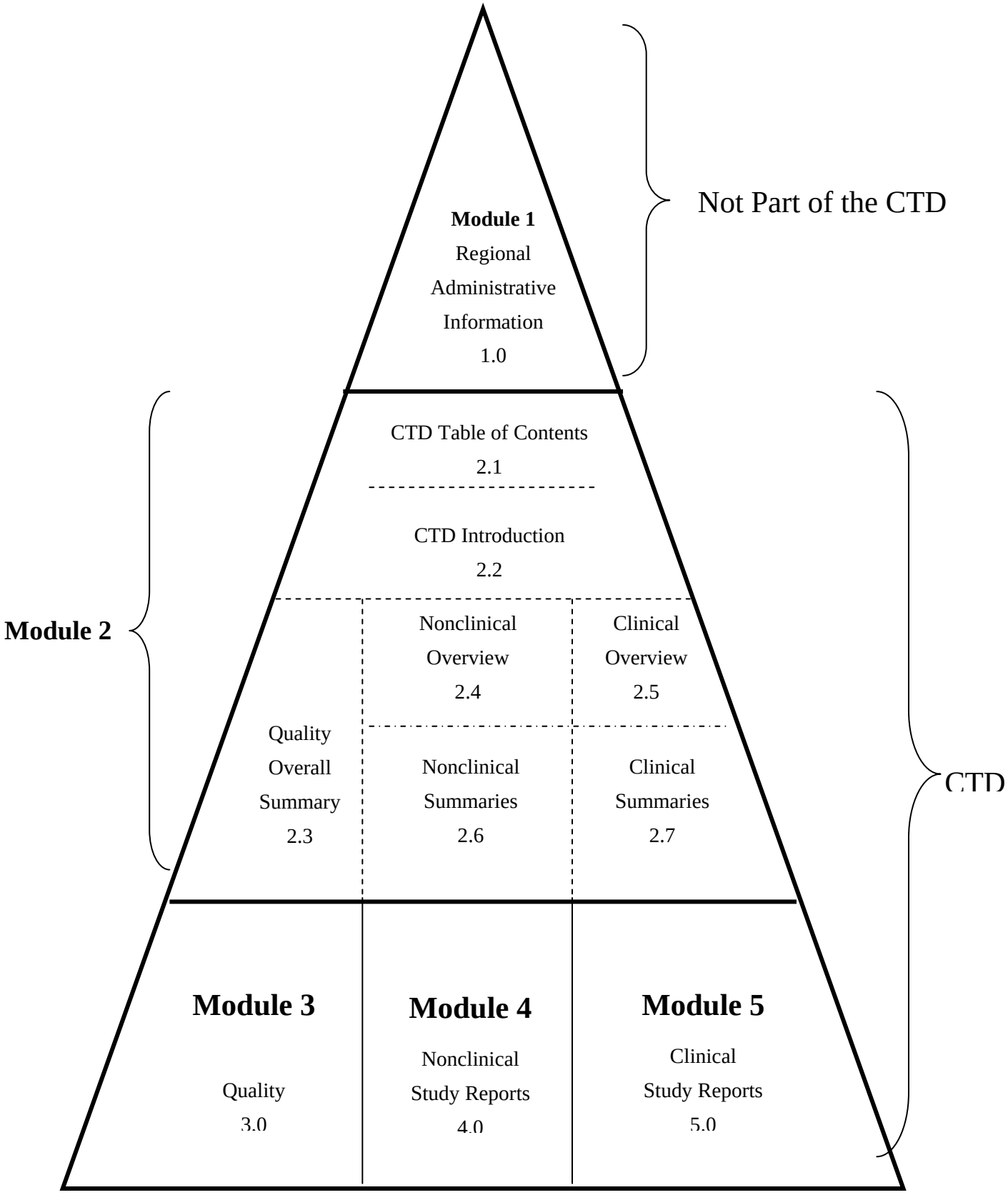
Chemical, Pharmaceutical and Biological documentation is provided by **Module 3**. This information should be structured as described in Guideline M4Q (M4Q (R1): QUALITY Module 2 :Quality Overall Summary (QOS) Module 3 : Quality The section of the application covering chemical and pharmaceutical data including data for biological/ biotechnological products).

The documentation on the Toxicological and Pharmacological Tests performed on drug/active substance and a drug/medicinal product is provided in the Non-clinical Written Summaries (from Module 2) and by the Non-clinical Study Reports **(Module 4).** These reports should be presented in the order described in Guideline M4S (M4S (R2): SAFETY Nonclinical Summaries and Organisation of Module 4 The non-clinical section of the application).

The documentation on the Clinical Trials performed on the drug/medicinal product is provided in the Clinical Written Summaries (from Module 2) and in the Clinical Study Reports **(Module 5)**. These reports should be presented in the order described in Guideline M4E (M4E (R1): EFFICACY Module 2 :Clinical Overview and Clinical Summary Module 5 Clinical Study Reports The clinical section of the Application).

http://www.ich.org/cache/compo/276-254-1.html

Diagrammatic Representation of the Organization of the CTD



Preparing and Organizing the CTD

Throughout the CTD, the display of information should be unambiguous and transparent, to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured through binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text. Acronyms and abbreviations should be defined the first time they are used in each module.

However when preparing the product information for applications in the centralised procedure (ref. Module 1.3.) it is mandatory to use the "QRD (Quality Review of Documents) convention".

Pagination and Segregation

Every document should be prepared in line with the CHMP /ICH/2887/99 Revision 1 Organisation CTD recommendation.

Information about national administrative requirements

Information about the addresses of the national authorities, the numbers of copies of dossier-modules required, and further information are published by the EC in the NTA, Vol. 2A, Chapter 7 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/ctd-chap7_2006-03.pdf).

Special guidance for different kind of applications

This international format is intended to apply to all categories of drug products / medicinal products (incl. NCE`s, radiopharmaceuticals, vaccines, herbals, etc.) and all types of applications (stand alone, generics, biosimilar etc.)), although some adaptations may be necessary for specific application/product types.

It is not designed to indicate what studies are required for successful approval, but to indicate an appropriate organization for the information included in the application. If no information is available or required under a specific heading, that section of the application should be marked “not applicable” or “not relevant” whilst retaining the section title and numbering, and, if necessary, a justification for the absence of a study should be provided in the Quality Overall Summary, the Non-clinical Overview and the Clinical Overview.

Applicants are reminded that for **bibliographical, generic and biosimilar, “hybrid” and extensions** the non-clinical/clinical overviews/summaries should focus on particular issues concerning the basis for the application. Applicants should also consult Chapter 1 of the NTA, Vol. 2A – Marketing authorisation.

For generic, biosimilar and “hybrid” applications and extensions cross-references to previous applications in the “old” EU-format will be accepted. No reformatting of already assessed and authorised “old” documentation into the CTD-format is necessary.

1. Bibliographical applications

For applications based upon **Article 10a of Directive 2001/83/EC,** non-clinical/clinical overviews/summaries should demonstrate that the constituent(s) of the medicinal product have a well-established use, with an acceptable level of safety and/or efficacy, as outlined in Annex I to Directive 2001/83/EC.

Tabulated clinical and non-clinical summaries in Module 2 shall be provided. Tables may not be necessary for very old, well known substances, but a proper justification will be required. Overviews always have to be provided.

2. Informed consent, Generic, “Hybrid” or Bio-similar applications

2 a) Consent from the marketing authorization holder

For applications based upon **Article 10c of Directive 2001/83/EC,** the original expert reports or quality/non-clinical/clinical overviews/summaries of the original marketing authorization holder may be referred to.

2 b) Applications relating to generic medicinal products and biosimilar medicinal products;

For applications according to **Article 10 (1), (3) and (4) Directive 2001/83/EC**, Module 2 must include the Quality Overall Summary, Non-clinical Overview and Clinical Overview. Non-clinical and Clinical Summaries can be provided, but they are only mandatory if new additional studies have been provided within the documentation.

3. Variation Applications in accordance with Regulation 1084/2003/EC and Regulation 1085/2003/EC

After 1st July 2003, all variation applications must be submitted using the EU-CTD format. However, cross-references to "old" EU-format documentation will be accepted, because the content is identical. Clear references to any "old" format documentation are essential.
*Example*s:

- Any new (either additional or revised) data in support of the variation must be submitted using the CTD format.
- If any data need to be submitted which are unchanged, for example, the Type I variation Guideline might specify the need for submission of a copy of the approved specifications, then the marketing authorisation holder should update the specifications into the new CTD-format. The marketing authorisation holder must also provide a declaration that the content of any reformatted documents is unchanged. Any future variation applications would then be able to use these "updated" (CTD) specifications.

Where only a cross-reference to already authorised data is required, such cross-references can still be made to the relevant "old" format dossier (Part and section). However, if the marketing authorisation holder prefers to take the opportunity to present the (unchanged) data in the new CTD-format instead, this would be equally acceptable as it would facilitate the handling of future variations. The marketing authorisation holder must also provide a declaration stating that the content of any reformatted documents is unchanged.

Type IA/IB Variation Applications and their supportive documentation – where appropriate – should be presented as follows

Where a cover letter is provided it should be placed in Module 1, 1.0 Cover Letter.

The checklist of conditions to be fulfilled and documentation to be supplied, i.e. the extract of the relevant page from the Guideline on Dossier Requirements for Type IA and Type IB notifications, should be placed in 1.2 Application Form after the Application Form itself.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

Documents should be assigned, wherever possible, to the relevant CTD section, primarily within Module 3 Quality and 1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet. These would include replacement sections and additional information.

Where documents cannot be assigned to specific CTD-defined locations then they should be included in 1.2 Application Form. These might include declarations, certificates, justifications etc. Where possible, they should be organised according to the Annexes for the Application Form for new products (Annexes 1 to 22). Where documents cannot be assigned to one of the annexes then it is appropriate to place them after the annexes. The 'Additional Data' section of Module 1 should not be used except for country-specific information defined

in Table 3.2 of Chapter 7, General Information, of the Notice to Applicants.

Documents should be presented with tab dividers for paper submissions or as separate files according to eCTD guidances.

Type II Variation Applications and their supportive documentation – where appropriate – should be presented as follows (non-exhaustive list depending on the scope of the variation and supportive data):

Module 1 :

1.0 Cover Letter
1.1 Comprehensive Table of Contents
1.2 Application Form
1.3 Product Information
1.3.1 SPC, Labelling and Package Leaflet – where appropriate
1.3.4 Consultation with Target Patient Population (e.g. in case of significant changes)
1.3.6 Braille (when Braille is implemented for an already authorised medicinal product as part of a variation)
1.4 Information about the Experts:
The relevant expert declaration(s) and signature(s) must be provided, corresponding to the Overview/Summary submitted in Module 2.
In cases where MAHs wish to distinguish this declaration from any previous declarations, the Variation Procedure Number of the RMS/EMEA may be included on top.
1.5 Specific Requirements for Different Types of Applications
1.5.3 (Extended) Data/Market Exclusivity
In case the applicant wants to claim a one-year data exclusivity at the time of the application for a new therapeutic indication, a document, justifying that the application concerns “a new therapeutic indication which is claimed to bring a significant clinical benefit” or that significant preclinical or clinical studies have been carried out, has to be provided.
Related study reports and supporting literature references shall be placed in the relevant Modules of the dossier and thus cross-referred to accordingly.
1.6 Environmental Risk Assessment (e.g. in case of a new indication with significant increase of the extent of use)
1.7. Orphan Market Exclusivity (in case the indication applied for is the same as an already authorised orphan medicinal product)
1.8.1 Pharmacovigilance system (e.g. in case of changes), where appropriate
1.8.2 Risk-Management System (e.g. in case of a significant change in indication)

1.9 Information relating to clinical trials (in case clinical trials supporting the variation application were carried out outside the EU)

Module 2:

As mentioned in the Variation Regulation any Type II variation should be accompanied by the relevant Overviews/Summaries updates or addenda (even if a variation is submitted at the request of the Competent Authority/CHMP). Expert details and signature are to be provided in Module 1.4 separated from the actual Overview/Summary.

Module 3, 4, 5:

Supportive data are to be included in Modules 3, 4 and/or 5 as appropriate and in accordance with the EU-CTD structure.

4. New Applications as referred to in Annex II of Regulation 1084/2003/EC and Regulation 1085/2003/EC ("Extensions").

The non-clinical/clinical overviews/summaries should particularly focus on the following elements:

- an evaluation of the results of the additional studies. The results should be discussed in the perspective of what is known from published literature and previous submissions. Additional studies should also be submitted in tabular formats provided in this Notice to Applicants ;
- if applicable an update of published literature relevant to the substance and the present application. The documentation may include annotated articles published in "peer review" journals, which may be acceptable for this purpose;
- every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

After 1st July 2003, all applications for extensions must also be submitted using the new EU-CTD format. However, references can be made to already assessed and authorised "old" Parts of the dossier, but only if no new additional data are submitted in these parts. In such cases, it is not necessary to reformat already assessed and authorised "old" documentation.

Modules 1 and 2 always have to be provided. Where no new clinical and/or non-clinical data are submitted the respective overviews/summaries can be replaced by expert-statements. It is however necessary to provide new CTD-format summaries and overviews to cover any new information or data provided in support of the application. In these CTD-format summaries/overviews, all the headings (numbers and titles) must be included, but where cross-references can be made, as the data has not changed, it is sufficient to include a statement such as "Not changed" (or similar).

Marketing authorisation holders are also encouraged, in addition to presenting the new extension quality data in the CTD-format, to reformat the entire assessed and authorised "old" format Part II into the new CTD-format, in order to obtain a complete CTD Module 3, covering all strengths/pharmaceutical forms.
Exceptionally, in those cases where there are multiple strengths and/or pharmaceutical forms, the Quality module of the extension may include only the data for the new strength/pharmaceutical form and cross-refer to the relevant "old" quality data. At the occasion of the next variation affecting the "old" part, marketing authorisation holders

should "reformat" (at least) that part into the CTD format.

5. Renewal Applications:

Since 1st July 2003 all applications for renewals must be submitted using the EU-CTD format. The guidance stated in the relevant guidelines/recommendations on the processing of renewals, have to be taken into account.
See Vol. 2C, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

Special guidance on herbal medicinal products

For the purposes of this document the terms "herbal substances and preparations" shall be considered equivalent to the terms "herbal drugs and herbal drug preparations", as defined in the European Pharmacopoeia.

For ease of reference the section titles of Modules 2 and 3 have been copied. The text following the section titles is intended to be explanatory and illustrative to herbal medicinal products only. The content of these sections should include relevant information described in Guidelines published by the Agency.

Click here to obtain the specific information on Modules 2 and 3 for herbal medicinal products:

- Module 2
- Module 3

Information relevant to the Active Substance Master File (ASMF)

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According to the current EU guideline on the ASMF procedure (Active Substance Master File guideline (CHMP QWP/227/02)[3] it is the responsibility of the applicant for a marketing authorisation for a medicinal product to ensure that the complete ASMF, that is both the applicant's ("open") part and the active substance manufacturer's restricted ("closed") part with original signed Letter of Access is supplied to the authorities directly by the active substance manufacturer in the CTD format, synchronised to arrive at around the same time as the marketing authorisation application. A copy of the "Letter of Access" shall be included in Annex 6.10 of the application form, in Module 1 and addressed to the regulatory authority to where the application is made. The applicant's ("open") part of the ASMF should be included in section 3.2.S of the Quality documentation presented in the CTD-format.

The active substance manufacturer's restricted ("closed") part of the ASMF should follow the structure of Module 3.2.S of the CTD. A separate Quality Overall Summary for the information included in the active substance manufacturer's restricted ("closed") part should also be provided, as part of the ASMF.

When an ASMF is provided as part of a new application for which the Quality data are submitted in the EU-CTD format, the complete ASMF (open and closed part and the Quality Overall Summary on the ASMF) must also be presented in the EU-CTD format.

[3] Former European Drug Master File (EDMF) CPMP/QWP/227/02 Guideline on Active Substance Master File procedure http://www.emea.eu.int/htms/human/qwp/qwpdraft.htm

Variation of an ASMF:

If a change concerns a section of an ASMF, the documentation for this change must be submitted in the CTD-format. The ASMF-holder should be strongly encouraged to reformat the complete ASMF at this occasion. This will facilitate the handling of changes/variations which affect data in the ASMF concerned.

The ASMF-holder should make a clear distinction between the

- reformatting of the ASMF data, already assessed by the competent authorities and
- the new documentation supporting the change to ASMF-data.

If an ASMF is reformatted into the new EU-CTD-format without any change in data, a signed declaration must be provided by the ASMF-holder certifying that the content of that ASMF is identical to the currently held version of the ASMF.

After reformatting of the ASMF, the new “open part” of the ASMF in CTD-format has to be sent by the ASMF-holder to the MAHs concerned, in order that the MAH is able to update all marketing authorisations where that ASMF has been used. It will be acceptable to have the ASMF in the CTD format, without reformatting of the corresponding Quality data in the dossier of the medicinal product.

If there is a change to the ASMF-data, the corresponding variation has to be submitted to the authorities by the MAH. For extension applications to MAs where an ASMF is used, the ASMF Holder should reformat the complete ASMF into the EU-CTD-format so that the ”new” format ASMF can be included in the extension application, rather than any cross reference being made to an “old” format ASMF.

European Certificate of Suitability of monographs of the European Pharmacopoeia

(CEP)

Applicants may use the CEP- scheme to replace some of the information needed in Module 3 for drug substances described in the European Pharmacopoeia..

The Drug Substance section should refer to the Certificate of Suitability in the relevant sections in Module 3.2.S. The Certificates of Suitability are deemed to replace the data of the corresponding sections and therefore no further additional information is necessary except concerning technical characteristics of the substance where not covered by the Certificate of Suitability (e.g. when the Certificate of Suitability does not describe a specific technical grade).

A complete copy of the Certificates of Suitability (including any annexes) should be provided in the annex 6.10 of the application form in Module 1 and in Module 3 R.

TSE-compliance can also be demonstrated by a CEP.

European Community Guidelines on Quality, Safety and Efficacy

In assembling the dossier for application for marketing authorisation, applicants are required to take into account the Community guidelines relating to the quality, safety and efficacy of drug/medicinal products published by the Commission in "The rules governing medicinal products in the European Community", Volumes 3A, 3B, 3C: Guidelines on the quality, safety and efficacy of drug/medicinal products for human use, and subsequent updates as adopted by the Committee for Human Medicinal Products. The guidelines adopted within the ICH process are considered as Community guidelines once adopted by the CHMP and published. References to the relevant Community or ICH guidelines have been included either within the relevant sections, or as annexes to each part of the dossier. For the latest updates of Community / ICH guidelines, applicants are advised to consult the Website of the EMEA on http://www.emea.eu.int/index/indexh1.htm (Regulatory Guidance and Procedures - Notes for Guidance).

With respect to the quality part of the dossier, the monographs and general chapters of the European Pharmacopoeia are also applicable. All materials of ruminant origin have also to comply with the TSE requirements.

Correlation Table:

EU-CTD (NTA, Vol. 2B, edition May 2006) vs. NTA, Vol. 2B (edition 1998)

MODULE 1 - ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2006)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
1.0	Cover Letter		
1.1	Comprehensive table of content	---	
1.2	Application Form	Administrative Data	I A
1.3	Product Information	Summary of Product Characteristics, Labelling and Package Leaflet	I B
1.3.1	Summary of Product Characteristics, Labelling and Package Leaflet	Summary of Product Characteristics	I B 1
		Proposal for packaging, labelling & package leaflet	I B 2
1.3.2	Mock-up		I B 2
1.3.3	Specimen		
1.3.4	Consultation with Target Patient Groups		
1.3.5	Product Information already approved in the Member States	SPCs already approved in the Member States	I B 3
1.3.6	Braille		
1.4	Information about the Experts	Expert Reports: Signature of Experts	I C
1.4.1	Quality		
1.4.2	Non-clinical		
1.4.3	Clinical		
1.5	Specific Requirements for different types of applications	---	
1.5.1	Information for bibliographical applications	---	
1.5.2	Information for Generic, “Hybrid” or Bio-similar Applications	---	
1.5.3	(Extended) Data/Market Exclusivity		
1.5.4	Exceptional Circumstances		
1.5.5	Conditional Marketing Authorisation		
1.6	Environmental risk assessment	Environmental risk assessment	
1.6.1	Non-GMO	Environmental risk assessment / ecotoxicity *(for non-GMOs)*	III R
1.6.2	GMO	Data related to the environmental risk assessment for products containing, or consisting of genetically modified organisms (GMOs)	II H
1.7	Information relating to Orphan Market Exclusivity		
1.7.1	Similarity		
1.7.2	Market Exclusivity		
1.8	Information relating to Pharmacovigilance		
1.8.1	Pharmacovigilance System		
1.8.2	Risk-management System		
1.9	Information relating to Clinical Trials		
	Responses to Questions	Responses to Questions	

MODULE 1 - ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2006)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
	Additional Data	Additional Data	

MODULE 2 - COMMON TECHNICAL DOCUMENT SUMMARIES			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
2.1	Overall CTD Table of Contents of Modules 2, 3, 4, and 5	Table of Contents for remainder of the dossier	I.A
2.2	Introduction	Product profile	I.C
2.3	Quality Overall Summary	Expert report on the chemical, pharmaceutical and biological documentation	I C 1
2.4	Non-clinical Overview	Expert Report on the toxico-pharmacological documentation	I C 2
2.5	Clinical Overview	Expert Report on the Clinical Documentation	I C 3
2.6	Non-clinical Summary	Appendices to the toxico-pharmacological Expert Report	I C 2
2.6.1	Pharmacology Written Summary	Written Summary	I C 2
2.6.2	Pharmacology Tabulated Summary	Tabular Formats	I C 2
2.6.3	Pharmacokinetics Written Summary	Written Summary	I C 2
2.6.4	Pharmacokinetics Tabulated Summary	Tabular Formats	I C 2
2.6.5	Toxicology Written Summary	---	---
2.6.6	Toxicology Tabulated Summary	Tabular Formats	I C 2
2.7	Clinical Summary	Appendices to the clinical Expert Report	I C 3
2.7.1	Summary of biopharmaceutics and associated analytical methods	Written Summary	I C 3
2.7.2	Summary of clinical pharmacology studies	Written Summary	I C 3
2.7.3	Summary of clinical efficacy	Written Summary	I C 3
2.7.4	Summary of clinical safety	Written Summary	I C 3
2.7.5	Synopses of Individual Studies	Tabular Formats	I C 3

MODULE 3 – QUALITY			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
3.1	MODULE 3 TABLE OF CONTENTS	---	---
3.2	BODY OF DATA	Chemical, Pharmaceutical, Biological Documentation	II
3.2.S	DRUG SUBSTANCE		
3.2.S.1	General Information	Scientific Data	II C 1.2
3.2.S.1.1	Nomenclature	Nomenclature	II C 1.2.1
3.2.S.1.2	Structure	Description: Structural formula	II C 1.2.2
3.2.S.1.3	General Properties	Physico-chemical characterization	II C 1.2.5
3.2.S.2	Manufacture	Manufacture	II C 1.2.3
3.2.S.2.1	Manufacturer(s)	Name(s) address(es) of the manufacturing source(s)	II C 1.2.3
3.2.S.2.2	Description of manufacturing process and process controls	Synthetic or manufacturing route Description of process	II C 1.2.3
3.2.S.2.3	Control of materials	Quality control during manufacture	II C 1.2.4
3.2.S.2.4	Controls of critical steps and intermediates	Quality control during manufacture	II C 1.2.4
3.2.S.2.5	Process validation and/or evaluation	---	---
3.2.S.2.6	Manufacturing process development	---	
3.2.S.3	Characterisation		
3.2.S.3.1	Elucidation of structure and other characteristics	Development chemistry	II C 1.2.5
3.2.S.3.2	Impurities	Impurities	II C 1.2.6
3.2.S.4	Control of drug substance	Specifications and routine tests	II C 1.1
3.2.S.4.1	Specification	Specifications and routine tests	II C 1.1
3.2.S.4.2	Analytical Procedures	Specifications and routine tests	II C 1.1

MODULE 3 – QUALITY			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
3.2.S.4.3	Validation of analytical procedures	Development Chemistry: Analytical Validation	II C 1.2.5
3.2.S.4.4	Batch analyses	Batch analysis	II C 1.2.7
3.2.S.4.5	Justification of Specification	Development Chemistry: Comments on the choice of routine tests and standards	II C 1.2.5
3.2.S.5	Reference Standards or Materials	Development chemistry: Full characterization of the primary reference material Batch analysis: Reference material	II C 1.2.5 II C 1.2.7
3.2.S.6	Container Closure System	---	
3.2.S.7	Stability	Stability Tests on Active Substance(s)	II F 1
3.2.P	DRUG PRODUCT		
3.2.P.1	Description and composition of the drug product	Composition and container (brief description)	II A1 II A2
3.2.P.2	Pharmaceutical Development	Development Pharmaceutics and clinical trial formulae	II A 4 II A3
3.2.P.2.4	Controls and critical steps and intermediates	Manufacturing process (including in-process control and phamraceutical assembly process) Control tests on intermediate products	II B3 II D
3.2.P.3	Manufacture	Method of Preparation	II B
3.2.P.3.1	Manufacturer(s)	Administrative Data	I A
3.2.P.3.2	Batch formula	Manufacturing Formula	II B 1
3.2.P.3.3	Description of Manufacturing Process and Process Controls	Manufacturing Process (including In-process Control and Pharmaceutical Assembly Process)	II B 2
3.2.P.3.4	Controls of critical steps and intermediates	Manufacturing Process (including In-process Control and Pharmaceutical Assembly Process)	II B 2
3.2.P.3.5	Process validation and / or evaluation	Validation of the Process	II B 3
3.2.P.4	Control of excipients	Excipients(s)	II C 2
3.2.P.4.1	Specifications	Specifications and routine tests	II C 2.1
3.2.P.4.2	Analytical procedures	Specifications and routine tests	II C 2.1
3.2.P.4.3	Validation of analytical procedures	Scientific data	II C 2.2
3.2.P.4.4	Justification of specifications	Scientific data	II C 2.2
3.2.P.4.5	Excipients of human or animal origin	---	
3.2.P.4.6	Novel Excipients *(ref to A 3)*	Excipient(s) not described in a pharmacopoeia Scientific data	II C 2.2.1 II C 2.2
3.2.P.5	Control of drug product	Control Tests on the Finished Product	II E
3.2.P.5.1	Specification(s)	Product specifications Quality specifications for the proposed shelf life	II E 1.1 II F 2
3.2.P.5.2	Analytical Procedures	Control Methods	II E 1.2
3.2.P.5.3	Validation of Analytical Procedures	Analytical validation of methods	II E 2.1
3.2.P.5.4	Batch analyses	Batch analysis	II E 2.2
3.2.P.5.5	Characterisation of Impurities	---	
3.2.P.5.6	Justification of specification(s)	Comments on the choice of routine tests and standards	II E 2.1
3.2.P.6	Reference Standards or Materials	Batch analysis: Reference material	II E 2.2
3.2.P.7	Container Closure System	Packaging Material (Immediate Packaging)	II C 3
3.2.P.8	Stability	Stability Tests on the Finished Product	II F 2
3.2.A	APPENDICES		
3.2.A.1	Facilities and Equipment	---	
3.2.A.2	Adventitious Agents Safety Evaluation	---	
3.2.A.3	Excipients	---	
3.2.R	REGIONAL INFORMATION	Validation of the process	-II B3--
3.3	LITERATURE REFERENCES	OTHER INFORMATION	II Q

MODULE 4 - NONCLINICAL STUDY REPORTS			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
4.1	MODULE 4 TABLE OF CONTENTS	---	---
4.2	STUDY REPORTS	TOXICO-PHARMACOLOGICAL DOCUMENTATION	III
4.2.1	PHARMACOLOGY	PHARMACODYNAMICS	III F
4.2.1.1	Primary pharmacodynamics	Pharmacodynamics effects relating to the proposed indications	III F 1
4.2.1.2	Secondary pharmacodynamics	General pharmacodynamics	III F 2
4.2.1.3	Safety pharmacology	General pharmacodynamics	III F 2
4.2.1.4	Pharmacodynamic drug interactions	Drug interactions	III F 3
4.2.2	PHARMACOKINETICS	PHARMACOKINETICS	III G
4.2.2.1	Analytical Methods and Validation Reports	Other Information	III Q
4.2.2.2	Absorption	Pharmacokinetics after a single dose Pharmacokinetics after repeated administration	III G 1 III G 2
4.2.2.3	Distribution	Distribution in normal and pregnant animals	III G 3
4.2.2.4	Metabolism	Biotransformation	III G 4
4.2.2.5	Excretion	Pharmacokinetics	III G 1, 2
4.2.2.6	Pharmacokinetic Drug Interactions (nonclinical)	---	
4.2.2.7	Other Pharmacokinetic Studies	---	
4.2.3	TOXICOLOGY	TOXICITY	III A
4.2.3.1	Single-dose toxicity	Single dose toxicity studies	III A 1
4.2.3.2	Repeat-dose toxicity	Repeated dose toxicity studies	III A 2
4.2.3.3	Genotoxicity	Mutagenic Potential	III D
4.2.3.4	Carcinogenicity	Carcinogenic Potential	III E
4.2.3.5	Reproductive and developmental toxicity	Reproductive Function Embryo-foetal and Perinatal Toxicity	III B III C
4.2.3.6	Local tolerance	Local Tolerance	III H
4.2.3.7	Other toxicity studies	Other Information	III Q
4.3	LITERATURE REFERENCES	OTHER INFORMATION	III Q

MODULE 5- CLINICAL STUDY REPORTS			
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**	**NTA**
5.1	MODULE 5 TABLE OF CONTENTS	---	---
5.2	TABULAR LISTINGS OF ALL CLINICAL STUDIES	EXPERT REPORT ON THE CLINICAL DOCUMENTATION, APPENDIX 2: WRITTEN SUMMARY – TABULAR OVERVIEW	I C 3
5.3	CLINICAL STUDY REPORTS	CLINICAL DOCUMENTATION	IV
5.3.1	Reports of Biopharmaceutic Studies	Pharmacokinetics	IV A 2
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	Pharmacokinetics	IV A 2
5.3.3	Reports of human pharmacokinetic (PK) studies	Pharmacokinetics	IV A 2
5.3.4	Reports of human pharmacodynamic (PD) studies	Pharmacodynamics	IV A 1
5.3.5	Reports of efficacy and safety studies	Clinical Trials	IV B 1
5.3.6	Reports of post-marketing experience	Post-marketing experience (if available)	IV B 2
5.3.7	Case report forms and individual patient listings, when submitted	*Appendix to each clinical study report, when submitted (Appendix 16.3)*	IV B 1
5.4	LITERATURE REFERENCES	PUBLISHED AND UNPUBLISHED EXPERIENCE (OTHER THAN 1) OTHER INFORMATION	IV B 3 IV Q

Module 1
European Union (EU)

Administrative Information and Prescribing Information

Edition May 2008

Module 1 Table of Content

1.7 Information relating to Orphan Market Exclusivity

1.7.1 Similarity
1.7.2 Market Exclusivity

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System
1.8.2 Risk-management System

1.9 Information relating to Clinical Trials

1.10 Information relating to Paediatrics

Responses to Questions

Additional Data

1.0 Cover Letter

The cover letter to the application should be included here.
Where necessary, a “Notes to Reviewers” document could be provided as an Appendix to the cover letter, providing further information in order to facilitate navigation (e.g. on hyperlinking, volumes presentation etc ….).

For paper submissions, only the relevant cover letter for the Member State concerned /EMEA should be provided.

1.1 Comprehensive Table of Contents

A comprehensive table of contents should be provided for each type of application, reflecting all module sections submitted as part of the application concerned. For New Applications, all sections should be addressed (see also 'introduction').
The Table of Contents should reflect the granularity of the dossier submitted, taking into account the Annex to the M4 ICH guideline on 'organisation of the CTD', published on:
http://www.ich.org

Module 1:

1.0 Cover Letter
1.1 Comprehensive Table of Contents
1.2 Application Form
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- 1.3.1 SPC, Labelling and Package Leaflet
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1.4 Information about the Experts
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1.5 Specific Requirements for Different Types of Applications
- 1.5.1 Information for Bibliographical Applications
- 1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
- 1.5.3 (Extended) Data / Market Exclusivity
- 1.5.4 Exceptional Circumstances
- 1.5.5 Conditional Marketing Authorisation

1.6 Environmental Risk Assessment
- 1.6.1 Non-GMO
- 1.6.2 GMO

1.7 Information relating to Orphan Market Exclusivity
- 1.7.1 Similarity
- 1.7.2 Market Exclusivity

1.8 Information relating to Pharmacovigilance
1.8.1 Pharmacovigilance System
1.8.2 Risk-management System
1.9 Information relating to Clinical Trials
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Responses to Questions
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Module 2: Common Technical Document Summaries

2.1 CTD Table of Contents (Module 2 – 5)
2.2 Introduction
2.3 Quality Overall Summary – Introduction
2.3.S Quality Overall Summary – Drug Substance
2.3.P Quality Overall Summary – Drug Product
2.3.A Quality Overall Summary – Appendices
2.3.R Quality Overall Summary – Regional Information
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries
2.6.1 Introduction
2.6.2 Pharmacology Written Summary
2.6.3 Pharmacology Tabulated Summary
2.6.4 Pharmacokinetics Written Summary
2.6.5 Pharmacokinetics Tabulated Summary
2.6.6 Toxicology Written Summary
2.6.7 Toxicology Tabulated Summary
2.7 Clinical Summaries
2.7.1 Summary of Biopharmaceutic and Associated Analytical Methods
2.7.2 Summary of Clinical Pharmacology Studies
2.7.3 Summary of Clinical Efficacy
2.7.4 Summary of Safety
2.7.5 References
2.7.6 Synopses of Individual Studies

Module 3: Quality

3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References

Module 4: Nonclinical Study Reports

4.1 Module 4 Table of Contents

4.2 Study Reports

4.3 Literature References

Module 5: Clinical Study Reports

5.1 Module 5 Table of Contents

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.4 Literature References

1.2 Application Form

Module 1.2 is to be used for an application for a marketing authorisation of a medicinal product for human use submitted to

(a) the European Medicines Agency under the centralised procedure or

(b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition or decentralised procedure.

The relevant application form has to be included, depending on the type of application.

The different application forms are available on the Website of the European Commission / DG Enterprise:

- *New Applications and Extension Applications*

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2b

- *Variation applications*

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c

- *Renewal applications*

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c

1.3 Product Information

In accordance with Article 8.3 (j), Article 11 and Title V of Directive 2001/83/EC applicants/marketing authorisation holders must include proposals for (revised) Summary of Product Characteristics (SPC), labelling and package leaflet in their application.

1.3.1 SPC, Labelling and Package Leaflet

The national competent authorities and the EMEA have published templates in all EU-languages (incl. Norwegian and Icelandic) for the presentation of product information (Summary of Product Characteristics (SPC), labelling and package leaflet):

- For mutual recognition or decentralised procedures: the templates for product information are published on the Heads of Agency website (annotated template) and on the EMEA website (clean templates)
  http://heads.medagencies.org/mrfg/docs/pi/QRD_annotated_template_CMDh.pdf
  http://www.emea.europa.eu/htms/human/qrd/qrdtemplate.htm

- For applications in the centralised procedure: the templates for product information are published on the EMEA website (annotated and clean templates)
  http://www.emea.europa.eu/htms/human/qrd/qrdtemplate.htm

  Product information must only be presented in the mandatory format and lay-out (see "QRD convention" on the EMEA Website) using the electronic product information templates provided on the EMEA Website.
  A complete set of SPC/Annex II/Labelling/Package Leaflet texts, as appropriate should be presented per language (in alphabetical order). Relevant guidance documents which address the submission and presentation of product information in paper and electronic format should be consulted when preparing this section of Module 1 (*e.g.* QRD Templates, EMEA Post-Authorisation Guidance document)

- For national procedures other national templates may apply

These templates should be used in conjunction with the relevant guidelines. In particular with the “Guideline on Summary of Product Characteristics”, the “Guideline on packaging information” and the “Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use", as published by the European Commission in the Notice To Applicants, Vol. 2C: (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c).

For the paper submission of product information:

- different language versions should be separated by a tab
- SPC, (Annex II), labelling and package leaflet should be separated by a tab
- for submission to CHMP members/Member States, only the relevant language version(s) are to be provided in addition to the English product information, as required.

1.3.2 Mock-up

In accordance with Directive 2001/83/EC, Article 8, a mock-up of the outer and immediate packaging of the medicinal product must be included with the application.

A “mock-up” is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/labelling of the medicinal product. It is generally referred to as a “paper copy” or “computer generated version”.

Requirements for mock-up and/or specimen submission are published by the European Commission in the Notice to Applicants, Vol. 2A, Chapter 7 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2a)

When mock-ups are submitted, a list detailing the mock-ups provided with the application should be included in addition to the actual mock-ups.

Module 1.3.3 Specimen

A “specimen” is a sample of the actual printed outer and immediate packaging materials and package leaflet.

Member States/EMEA may require specimens of the sales presentation of the medicinal product to be submitted, in order to check compliance with the relevant articles in Title V of Directive 2001/83/EC (e.g. Article 56).

Requirements for mock-up and/or specimen submission are published by the European Commission in the Notice to Applicants, Vol. 2A, Chapter 7 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2a)

When specimens are submitted, a list detailing the specimens provided should be included.
For the electronic submission of Module 1, only the list detailing the specimens should be included here, separate from the actual specimens provided.

1.3.4 Consultation with Target Patient Groups

Articles 59(3) and 61(1) of Directive 2001/83/EC require that the package leaflet reflects the results of consultations with target patient groups to ensure that it is legible, clear and easy to use, and that results of assessments carried out in cooperation with target patient groups be provided to the competent authority/EMEA.

These articles do not define the precise method to be used. As a consequence, these provisions permit ‘user testing’ as well as other appropriate forms of consultation.

This is addressed in the draft EU guidance document published on the website of the European Commission:
http://
ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/08_05/usertesting_20050817.pdf
which will be included in the Commission “Guideline on the readability of the label and package leaflet of medicinal products for human use”, (see Website of the European Commission: http:// ec.europa.eu/enterprise/pharmaceuticals /eudralex/homev2.htm#2c)

Information from the applicant regarding the ’user consultation’ performed together with the presentation of results, or a justification not performing such consultation, is to be included in this section for all new applications and for relevant post-authorisation applications introducing significant changes to the package leaflet.

Module 1.3.5 Product Information already approved in the Member States

(Where applicable)

Module 1.3.6 Braille

In accordance with Article 56a of Directive 2001/83/EC the name of the medicinal product must be expressed in Braille format on the packaging.

This is addressed in the European Commission guidance document published on the website of the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/04_05/braille_text20050411.pdf, which will be included in the Commission "Guideline on the readability of the label and package leaflet of medicinal products for human use", (see Website of the European Commission: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c)

Applicants should address here the proposed implementation of the Braille requirement on the packaging of the medicinal product concerned, based on the principles set-out in the above-mentioned European Commission guidance document. In addition, the Braille text (in normal font) which will be printed on the outer carton in Braille needs to be included in section 16 of the outer carton product information templates (if applicable) and should be indicated with dots on the mock-ups (where applicable and feasible).

1.4 Information about the Experts

In accordance with Article 12 of Directive 2001/83/EC experts must provide detailed reports of the documents and particulars which constitute Modules 3, 4 and 5.
In addition Article 12.1 and Part I 1.4 of Annex I of 2001/83/EC refer to signed expert reports for the different scientific parts of the dossiers.
The requirement for these signed Expert Reports may be met by providing:

- The Quality Overall Summary, Non-clinical Overview / Summary and Clinical Overview / Summary in Module 2,
- A declaration signed by the experts in Module 1.4.
- A brief information on the educational background, training and occupational experience in Module 1.4.

For post-authorisation applications, the relevant expert declaration(s) must be provided.
In cases where marketing authorisation holders wish to distinguish such declaration from any previous declarations, the relevant procedure number of the reference member state/EMEA may be included on top.

1.4.1 Quality

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC.

QUALITY :

Name of the expert: …….. Signature:

Address: ……..

……..

……..

……..

Date:

According to the Annex I of Directive 2001/83/EC brief information (*curriculum vitae*) on the educational background, training and occupational experience of the expert is attached.

1.4.2 Non-Clinical

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC

NONCLINICAL (pharmacology, pharmacokinetic, toxicology):

Name of the expert: …….. Signature:
Address: ……..
……..
……..
……..

Date:

According to the Annex I of Directive 2001/83/EC brief information (*curriculum vitae*) on the educational background, training and occupational experience of the expert is attached.

1.4.3 Clinical

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EC

CLINICAL:

Name of the expert: …….. Signature:
Address: ……..
……..
……..
……..

Date:

According to the Annex I of Directive 2001/83/EC brief information (*curriculum vitae*) on the educational background, training and occupational experience of the expert is attached.

1.5 Specific requirements for Different Types of Applications

1.5.1 Information for Bibliographical Applications

For bibliographical applications based upon Article 10a of Directive 2001/83/EC applicants should provide here a concise document (up to approximately 5 pages), summarizing the grounds and evidence used for demonstrating that the constituent(s) of the medicinal product have a well-established use, with an acceptable level of safety and efficacy, as outlined in Part II.1 of Annex I to Directive 2001/83/EC.

1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications

For applications based upon Article 10(1), 10(3) or 10(4) of Directive 2001/83/EC, applicants should provide here a concise document (up to approximately 5 pages), summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted, is:

- A 'generic' of a reference medicinal product (Art 10.1).

  This summary should include details on the medicinal product, its qualitative and quantitative composition in active substance(s), its pharmaceutical form and its safety/efficacy profile of the active substance(s) in comparison to the active substance(s) of the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and efficacy.

- A so-called 'hybrid' of a reference medicinal product (Art 10.3).

  This summary should include details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.

- A 'similar' biological medicinal product – a so-called 'biosimilar' (Art 10.4).

  This summary should include details on the similar biological medicinal product, its active substance, raw materials and manufacturing process. Differences with relevant attributes of the reference medicinal product should be included. Any other changes introduced during development which could affect comparability should be highlighted. The comparability exercise versus the reference medicinal product for quality, safety and efficacy should be described, and the reference medicinal product used throughout the quality, safety and efficacy development programme (as appropriate) should be defined. The table presented below should be completed and included in this section of Module 1.

No copy of the information already provided in the application form (Module 1.2) should be repeated here. However, further detailed information on the elements listed in the application form should be provided here where relevant.

OVERVIEW OF THE CHOSEN REFERENCE PRODUCT FOR COMPARABILITY

Applicant's product details
Product Name, Strength, Pharmaceutical Form: **Name of applicant:**

Overview of the chosen EU reference medicinal product used in the quality comparability exercise

Reference Product Name Strength, Pharmaceutical Form	Marketing Authorization number in EU (Specify country)	Country of Manufacture of the finished medicinal product	Country of Batch Release Site in EEA	Comment

Overview of the chosen reference medicinal product used in the non-clinical comparability exercise

Reference Product Name Strength, Pharmaceutical Form	Marketing Authorization number in EU (Specify country)	Country of Manufacture of the finished medicinal product	Country of Batch Release Site in EEA	Study No (+ Short mention of the nature of the study, e.g. PK, PD, toxicology.)	Comment

Overview of the chosen reference medicinal product used in the clinical comparability exercise

Reference Product Name Strength, Pharmaceutical Form	Marketing Authorization number in EU (Specify country)	Country of Manufacture of the finished medicinal product	Country of Batch Release Site in EEA	Study No (+ Short mention of the nature of the study, e.g. PK, PD, clinical efficacy, etc)	Comment

1.5.3 (Extended) Data / Market Exclusivity

This section is required in case the marketing authorisation holder/applicant wishes to claim (additional) data / market exclusivity when applying for a new indication or change in classification, based on the following legal provisions:

- In accordance with the fourth subparagraph of **Article 10(1)** of Directive 2001/83/EC and Article 14(11) of Regulation 726/2004, the 10- year period of marketing protection may be extended by one year in the event of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies.
- According to **Article 10(5)** of Directive 2001/83/EC a non-cumulative period of one year of data exclusivity may be granted for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies are carried out in relation to the new indication.
- According to **Article 74a** of Directive 2001/83/EC where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant or marketing authorisation holder for a change of classification of the same substance for one year after the initial change was authorised.

Requirements in relation to Article 10(1) of Directive 2001/83/EC and Article 14(11) of Regulation (EC) No 726/2004:

The marketing authorisation holder shall provide in this section a report justifying that the application concerns a new therapeutic indication that brings significant clinical benefit in comparison with existing therapies.

The report, which should in general be not more than 5-10 pages, should include:

- Justification of the proposed new indication compared to the therapeutic indication(s) already authorised.
- Details of existing therapies relating to the proposed new indication
- Justification as to why the medicinal product, for which extended marketing protection period is sought, is of significant clinical benefit in comparison to existing therapies in the new therapeutic indication.

Related study reports and literature references shall be placed in the relevant Modules of the dossier and cross-referred to accordingly.

Please also refer to the "Commission Guideline on elements required to support the significant clinical benefit in comparison with existing therapies of new therapeutic indication in order to benefit from an extended (11 years) Marketing Protection period" as published on the Commission's website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/guideline_14-11-2007.pdf).

Requirements in relation to Article 10(5) of Directive 2001/83/EC:

The marketing authorization holder/applicant shall provide in this section a report justifying that the application concerns a new therapeutic indication and that significant preclinical or clinical studies have been carried out in relation to this new indication.

The report, which should in general be not more than 5-10 pages, should include:

- Introduction.
- Justification of the new indication compared to the existing therapeutic indication(s).
- Justification that significant preclinical or clinical studies have been carried out in relation to this new indication.
- Justification that the substance can be considered as a "well-established substance" in accordance with the requirements of indent (a) in section 1 of Part II of the Annex to Directive 2001/83/EC.

Related study reports and literature references shall be placed in the relevant Modules of the dossier and cross-referred to accordingly.

Please also refer to the "Guideline on new therapeutic indication for a well-established substance" as published on the Commission's website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/10%20_5_%20guideline_11-2007.pdf)

Requirements in relation to Article 74a of Directive 2001/83/EC:

The marketing authorization holder/applicant shall provide in this section a report justifying that its application includes significant preclinical tests or clinical trials which have been carried out in relation to this change of classification.

The report, which should in general be not more than 5-10 pages, should include:

- A summary of the preclinical tests and/or clinical trials carried out in relation to the change of classification

- A justification why the preclinical tests or clinical trials carried out in relation to the change of classification should be viewed as significant.

Related study reports and literature references shall be placed in the relevant Modules of the dossier and cross-referred to accordingly.

Please also refer to the “Guideline on changing the classification for the supply of a medicinal product for human use” as published on the Commission’s Website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c)

1.5.4 Exceptional Circumstances

According to Article 22 of Directive 2001/83/EC and Article 14(7) of Regulation (EC) No 726/2004, an authorisation may be granted in exceptional circumstances subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. Such an authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Part II.6 of the Annex I to Directive 2001/83/EC.

If the applicant considers that the grounds for approval under exceptional circumstances should apply, the applicant should include a justification in this section, covering the following aspects.

1) A claim that the applicant can show that he is unable to provide comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use
2) A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided
3) Justification on the grounds for approval under exceptional circumstances
4) Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information)

Please also refer to the "Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14 (8) of Regulation (EC) No 726/2004" published on the EMEA website (http://www.emea.europa.eu/pdfs/human/euleg/35798105en.pdf)

1.5.5 Conditional Marketing Authorisation

This section is only applicable to applications in the centralised procedure.

Where the applicant requests a 'conditional marketing authorisation' to be granted in accordance with Article 14(7) of Regulation (EC) No 726/2004, the applicant should include a justification in this section, covering the following aspects:

- Evidence that the product falls under Article 3(1) or 3(2) of Regulation (EC) No 726/2004 and belongs to one of the categories set-out in Article 2 of Commission Regulation (EC) No 507/2006;
- Evidence that the product satisfies the requirements laid down in Article 4 of Commission Regulation (EC) No 507/2006;
- Applicant's proposal for completion of ongoing studies, conduct of new studies and/or collection of pharmacovigilance data (as appropriate), in accordance with Article 4(1)(b) of Commission Regulation (EC) No 507/2006.

Please also refer to the "Guideline on the scientific application and the practical arrangements on the Conditional Marketing Authorisation" published on the EMEA website (include link to doc on Website once published).

1.6 Environmental Risk Assessment

In accordance with Article 8 (ca) and (g) of Directive 2001/83/EC an application for marketing authorisation shall be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment.

The requirements in the Directive relate to those risks to the environment arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products.

For the paper submission of the application, extensive documentation for the environmental risk assessment should always be provided in a separate volume as part of Module 1. In case of a short statement, this can remain in the Module 1 volume(s).

1.6.1 Non-GMO

Applications for marketing authorisations for medicinal products which do not contain GMOs (Genetically Modified Organisms) should include in Module 1 an indication of any potential risks presented by the medicinal product for the environment.

A dated signature of the author, information on the author's educational, training and occupational experience (CV), and a statement of the author's relationship with the applicant, shall be provided.

Please also refer to the “Guideline on the Environmental Risk Assessment for medicinal products for human use” as published on the EMEA website (http://www.emea.europa.eu/pdfs/human/swp/444700en.pdf).

1.6.2 GMO

Applications for marketing authorisations for medicinal products which contain GMOs (Genetically Modified Organisms) should include in Module 1 an environmental risk assessment.

GMO means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.
Environmental risk assessment means the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.
The information shall consist of:

- an introduction;
- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;
- the complete technical dossier supplying the information required by Annexes III and IV t Directive 2001/18/EC;
- the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC;
- the results of any investigations performed for the purposes of research or development;
- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;
- appropriate measures in order to inform the public.

A dated signature of the author, information on the author's educational, training and occupational experience (CV), and a statement of the author's relationship with the applicant, shall be provided.

1.7 Information relating to Orphan Market Exclusivity

This section is required for **all new Applications** (not only for Designated Orphan medicinal products) as well as for Type II variations for new indications, where the indication applied for is the same as the indication of an authorised Orphan Medicinal Product.

In accordance with Article 8.1 of Regulation (EC) No 141/2000, where a marketing authorisation in respect of an orphan medicinal product has been granted in all Members States, the Community and the Member States shall not, for a period of 10 years, accept another application for marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the applicant must submit a report addressing the possible **"similarity"** with the authorised orphan medicinal product.
If the medicinal product, which is the subject of the application for marketing authorisation is deemed to be "similar" to an orphan medicinal product covered by the above-mentioned market exclusivity provisions, the applicant must furthermore provide justification that one of the **derogations** laid down in Article 8.3, paragraphs (a) to (c) of the same Regulation applies, that is:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or
(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

Further details can be found in the "European Commission guideline on aspects of the application of Article 8 of Regulation (EC) No 141/2000: Assessment of similarity and/or clinical superiority of orphan medicinal products when assessing marketing authorisation applications and variations." (include link to doc on Website once published)

1.7.1 Similarity

Where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, applicants should provide a critical report addressing the possible similarity with the authorised orphan medicinal product and concluding on similarity or “non” similarity.

1.7.2 Market Exclusivity

If the medicinal product, which is the subject of the application for marketing authorisation is deemed to be "similar" to an orphan medicinal product covered by the above-mentioned market exclusivity provisions, the applicant must furthermore provide justification that one of the **derogations** laid down in Article 8.3, paragraphs (a) to (c) of Regulation (EC) No 141/2000 applies, that is:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his **consent** to the second applicant, or

Where this derogation applies, a signed letter from the holder of authorised orphan medicinal product confirming his/her consent for the second applicant to file an application for marketing authorisation, in accordance with Article 8.3 (a) of the same Regulation, and with specific reference to this provision, should be provided.

(b) the holder of the marketing authorisation for the original orphan medicinal product is **unable to supply sufficient quantities** of the medicinal product, or

Where this derogation applies, applicants should provide a report describing why supply of the authorised orphan medicinal product is deemed to be insufficient, in accordance with Article 8.3 (b) of Regulation (EC) No 141/2000. The report should include details of the supply shortage and justify that as a result patients' needs in the orphan indication are not being met. All claims should be substantiated by qualitative and quantitative references.

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise **clinically superior**.

Where this derogation applies, applicants should provide a critical report justifying why the medicinal product which is the scope of the application is deemed to be "clinically superior" to the authorised orphan medicinal product, in accordance with Article 8.3 (c) of Regulation (EC) No 141/2000 and Article 3.3(d) of Regulation (EC) No 847/2000.

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System

According to Article 8 (ia) of Directive 2001/83/EC a detailed description of the pharmacovigilance system which the applicant will introduce must be provided.
This should include proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country according to Article 8 (n) of Directive 2001/83/EC).

The description of the marketing authorisation holder's pharmacovigilance system should follow the requirements and format as detailed in Volume 9A of Eudralex (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm).

1.8.2 Risk-management System

According to Article 8 (ia) of Directive 2001/83/EC a detailed description of the risk-management system which the applicant will introduce should be provided, where appropriate.

The detailed description of a risk management system should be provided in the form of an EU Risk Management Plan (EU-RMP), as outlined in Volume 9A of Eudralex (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm).

The EU-RMP contains 2 parts:
Part I
- A Safety Specification
- A Pharmacovigilance Plan, and

Part II
- An evaluation of the need for risk minimisation activities,

and if there is a need for additional (ie non- routine) risk minimisation activities:
- A risk minimisation plan

An EU-RMP may need to be submitted at any time of a product's life-cycle, ie during both the pre-authorisation and post-authorisation phases. In particular an EU-RMP should be submitted:

- with the application for a **new marketing authorisation** for :
  - any product containing a new active substance
  - a similar biological medicinal product
  - a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product
- with an application involving a **significant change** in a marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication) unless it has been agreed with the competent authority that submission is not required.
- on **request** from a competent authority (both pre-and post- authorisation).
- on the **initiative** of a applicant/marketing authorisation holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new authorisation may require an EU-RMP:

- known active substances
- hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks
- bibliographical applications
- fixed combination applications.

It is strongly recommended that discussions with the competent authorities on the need for, and content of, an EU-RMP should take place in advance of submission, especially for situations where the submission of an EU-RMP is not mandatory.

The RMP should be presented in a stand-alone format (separate volumes in paper) allowing circulation to, and evaluation by pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable.

1.9 Information relating to Clinical Trials

According to Article 8 (ib) of Directive 2001/83/EC a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC should be provided, where applicable.

This statement should indicate that “clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC” together with a listing of all trials (protocol number) and third countries involved.

The requirement applies to **all new applications** (including extension applications), and **other** relevant post-authorisation regulatory procedures (e.g. variations) for which clinical trial reports are submitted.

1.10 Information relating to Paediatrics

With reference to Article 7, 8 and 30 of Regulation (EC) No 1901/2006 ('paediatric regulation'), this section is required:

- as of 26 July 2008 for **all new Applications**[*] for a medicinal product which is not authorised in the EEA
- as of 26 January 2009 for applications[*] for **new indications, new pharmaceutical forms and new routes of administration**, for authorised medicinal products which are protected either by a supplementary protection certificate, or by a patent which qualifies for the granting of such a certificate.
- for Paediatric Use marketing authorisation applications (**PUMA**)

In accordance with Article 23 of Regulation (EC) No 1901/2006 ('paediatric regulation'), the competent authority responsible for granting marketing authorisations shall verify whether an application for marketing authorisation, extension or variation complies with the requirements laid down in article 7 or 8 of that Regulation, or whether a PUMA application complies with the agreed Paediatric Investigation Plan (PIP).

For guidance on PIPs, please refer to the draft "Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies", as published by the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/draft_guideline_pip_2007-02.pdf).

Applicants should therefore include the following documents in this section, as appropriate:
- copy of the product-specific waiver decision issued by the EMEA;
or
- copy of the class-waiver decision issued by the EMEA;
or
- copy of the latest version of the PIP Decision(s) (incl. deferrals, if applicable), together with -if available-:

[*]except for generic, hybrid, bio-similar and well-established use applications and traditional herbal or homeopathic medicinal products (see Article 9 of the paediatric regulation)

- A copy of the PDCO opinion on PIP compliance + report (in case PIP compliance verification by PDCO has taken place)
- The applicant's "PIP Compliance Report" (in case no competent authority compliance verification has taken place). Please also refer to the Template for such PIP compliance reports published on the EMEA website (include link to doc on Website once published). Related study reports should be placed in the relevant Modules of the dossier and cross-referred to accordingly.
- Overview table of the PIP results, indicating in which application(s) they were/are going to be submitted, status of the application(s), as well as their location in the present application.

Responses to Questions

When submitting responses to questions (e.g. at Day 121 in the Centralised Procedure or at Day 60 in the MRP) applicants are advised to include in this section a document which lists the questions with the corresponding narrative text response for each question.

Where responses also contain new or updated data/documents relating to Modules 3, 4 and/or 5, such data/documents should be placed in the relevant sections of those Modules. This may also apply to Module 1 (e.g. revised product information), as well as to Module 2 in cases where extensive data/documents would require inclusion of the relevant summaries and/or overview sections.

Additional Data

This section is required for national, mutual recognition and decentralised applications only.

In accordance with the relevant national legislation and practices, and as detailed in Chapter 7 of the Notice to Applications, additional data may need to be provided as part of a national, decentralised or mutual recognition application.

Member State specific requirements for such additional data can be found on the Website of the European Commission / DG Enterprise:
http://ec.europa.eu /enterprise/pharmaceuticals/eudralex/homev2.htm#2a
For the paper submission of the application, only the additional data relevant to the Member State concerned should be provided in this section, in the order as listed in Chapter 7 for the Member State concerned, as appropriate.

Note: If such data relate to Modules 2, 3, 4 and/or 5, the documents should also be placed in the relevant sections of those Modules.

Module 2

Common Technical Document Summaries

NTA, Volume 2B, CTD-Module 2

Edition July 2003

Module 2.1
Common Technical Document Table of Contents (Modules 2 – 5)

Module 2.2
Introduction

The general introduction to the medicinal product should include its pharmacological class, mode of action and the proposed clinical use. In general the introduction should not exceed one page.

Module 2.3
Quality Overall Summary

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules.

This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

The *italicised* text below indicates where tables, figures, or other items can be imported directly from Module 3.

INTRODUCTION
The introduction should include proprietary name, non-proprietary name, European Pharmacopoeia name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration according to the current version of the Standard Terms of the European Pharmacopoeia and proposed indication(s)

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, manufacturer)

Information from 3.2.S.2 should be included:

- Information on the manufacturer;

- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- *A flow diagram, as provided in 3.2.S.2.2;*
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterisation (name, manufacturer)

For NCE:

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

For NCE and Biotech:

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance (name, manufacturer)

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials (name, manufacturer)

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (name, manufacturer)

A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (name, manufacturer)

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (name, dosage form)

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, dosage form)

Information from 3.2.P.3 should include:

- Information on the manufacturer.
- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.
- *A flow diagram, as provided under 3.2.P.3.3.*
- A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (name, dosage form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (name, dosage form)

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (name, dosage form)

A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (name, dosage form)

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

Biotech:
A summary of facility information described under 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

2.3.A.3 Excipients

2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

Module 2.4
Nonclinical Overview

NONCLINICAL OVERVIEW

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

General Aspects

The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidelines. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries, in the following format: (Table X.X, Study/Report Number).

Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

Overview of the nonclinical testing strategy
Pharmacology
Pharmacokinetics
Toxicology
Integrated overview and conclusions
List of literature references

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, anti-product antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to:

- pharmacodynamics
- toxic signs
- causes of death
- pathologic findings
- genotoxic activity - the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- the carcinogenic risk to humans - if epidemiologic data are available, they should be taken into account
- fertility, embryofetal development, pre-and post-natal toxicity
- studies in juvenile animals
- the consequences of use before and during pregnancy, during lactation, and during pediatric development
- local tolerance
- other toxicity studies/ studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect / phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- animal species used
- numbers of animals used
- routes of administration employed
- dosages used
- duration of treatment or of the study
- systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended.
- the effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

Module 2.5
Clinical Overview

Preamble

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarisation of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

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, analyse 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, ; 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 in Module 5 is encouraged.

Table of Contents

Detailed Discussion of Content of the Clinical Overview Sections

2.5.1 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 product is 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. Briefly describe plans for the use of foreign clinical data (ICH E5).
- 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. Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.5.2 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).

2.5.3 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 CTD. 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 summarised in section 2.7.2.4 of the Clinical Summary.

2.5.4 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).
- support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).
- 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.

2.5.5 Overview of Safety

The purpose of this section is to provide a concise critical analysis of the safety 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 should be 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 other members 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 test drug 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, rebound phenomena 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.
- support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

2.5.6 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.

2.5.7 Literature References

A list of references used, stated in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE) [1] or the system used in "Chemical Abstracts", should be provided. Copies of all references cited in the Clinical Overview should be provided in Section 5.4 of Module 5.

[1] The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

Module 2.6
Nonclinical Summary

NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Guidance on Nonclinical Written Summaries

Introduction

This guidance is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format. This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasised that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

General Presentation Issues

Order of Presentation of Information Within Sections

When available, in vitro studies should precede in vivo studies. Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Non-human primate
- Other non-rodent mammal
- Non-mammals

Routes of administration should be ordered as follows:

- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures. Examples of formats that might be included in the Written Summaries are shown in Appendix A.

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries

Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100-150 pages.

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetcs
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Guidance on Nonclinical Tabulated Summaries

It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined in this guidance. Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

This guidance is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed. Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are provided in Appendices B and C, which follow. Appendix B contains templates for use in preparation of the tables. The templates are annotated (in italics) to provide guidance on their preparation. (The italicized information should be deleted when the tables are prepared.) Appendix C provides examples of the summary tables. The purpose of the examples is to provide additional guidance on the suggested content and format of the Tabulated Summaries. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product. Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information. Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

When a juvenile-animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

CONTENT OF NONCLINICAL WRITTEN AND TABULATED SUMMARIES

2.6.1 INTRODUCTION

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

- Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties;
- Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

2.6.2 PHARMACOLOGY WRITTEN SUMMARY

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief summary
- Primary pharmacodynamics
- Secondary pharmacodynamics
- Safety pharmacology
- Pharmacodynamic drug interactions
- Discussion and conclusions
- Tables and figures (either here or included in text)

2.6.2.1 Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

2.6.2.2 Primary Pharmacodynamics

Studies on primary pharmacodynamics* should be summarised and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

2.6.2.3 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics* should be summarised by organ system, where appropriate, and* evaluated in this section.

2.6.2.4 Safety Pharmacology

Safety pharmacology studies* should be summarised and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary pharmacodynamic studies should be considered along with safety pharmacology studies.

2.6.2.5 Pharmacodynamic Drug Interactions

If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.

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* See ICH Guideline S7, *Safety Pharmacology Studies for Human Pharmaceuticals*, Note 2. p. 8, for definitions.

2.6.2.6 Discussion and Conclusions

This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise.

2.6.2.7 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.6.3 PHARMACOLOGY TABULATED SUMMARY (SEE APPENDIX B)

2.6.4 PHARMACOKINETICS WRITTEN SUMMARY

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Methods of Analysis
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.4.1 Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasising, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

2.6.4.2 Methods of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

2.6.4.3 Absorption

The following data should be summarised in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies)

2.6.4.4 Distribution

The following data should be summarised in this section:

- Tissue distribution studies
- Protein binding and distribution in blood cells

- Placental transfer studies

2.6.4.5 Metabolism (interspecies comparison)

The following data should be summarised in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Pre-systemic metabolism (GI/hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition

2.6.4.6 Excretion

The following data should be summarised in this section:

- Routes and extent of excretion
- Excretion in milk

2.6.4.7 Pharmacokinetic Drug Interactions

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarised in this section.

2.6.4.8 Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarised in this section.

2.6.4.9 Discussion and Conclusions

This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.

2.6.4.10 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY (SEE APPENDIX B)

2.6.6 TOXICOLOGY WRITTEN SUMMARY

The sequence of the Toxicology Written Summary should be as follows:

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Studies in Juvenile Animals
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.6.1 Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than 6). In this section, the extent of the toxicologic evaluation can be indicated by the use of a table listing the principal toxicologic studies (results should not be presented in this table), for example:

TOXICOLOGY PROGRAMME

Study type and duration	Route of administration	Species	Compound administered*
Single-dose toxicity	po and iv	Rat and mouse	Parent drug
Single-dose toxicity	po and iv	Rat and mouse	Metabolite X
Repeat-dose toxicity			
1 month	po	Rat and dog	Parent drug
6 months	po	Rat	" "
9 months,	po	Dog	" "
etc.			

* This column required only if metabolite(s) are investigated.

The scope of the toxicologic evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

2.6.6.2 Single-Dose Toxicity

The single-dose data should be very briefly summarised, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.

2.6.6.3 Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)

Studies should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/response relationships, no observed adverse effect levels, etc.). Non-pivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).

2.6.6.4 Genotoxicity

Studies should be briefly summarised in the following order:

- *in vitro* non-mammalian cell system
- *in vitro* mammalian cell system
- *in vivo* mammalian system (including supportive toxicokinetics evaluation)
- other systems

2.6.6.5 Carcinogenicity (including supportive toxicokinetics evaluations)

A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarised in the following order:

- Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Other studies

2.6.6.6 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations)

Studies should be summarised in the following order, giving brief details of the methodology and highlighting important findings:

- Fertility and early embryonic development
- Embryo-fetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted.

If modified study designs are used, the sub-headings should be modified accordingly.

2.6.6.7 Local Tolerance

If local tolerance studies have been performed, they should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.

2.6.6.8 Other Toxicity Studies (if available)

If other studies have been performed, they should be summarised. When appropriate, the rationale for conducting the studies should be provided.

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Studies on metabolites
- Studies on impurities
- Other studies

2.6.6.9 Discussion and Conclusions

This section should provide an opportunity to discuss the toxicologic evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.

2.6.6.10 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.6.7 TOXICOLOGY TABULATED SUMMARY (SEE APPENDIX B)

APPENDIX A: EXAMPLES OF TABLES AND FIGURES FOR WRITTEN SUMMARIES

The tables and figures in Appendix A are presented merely as examples. Applicants should provide tables and figures using a format appropriate to the product.

Study references should be included in the table or text.

Tables should include statistics, if appropriate.

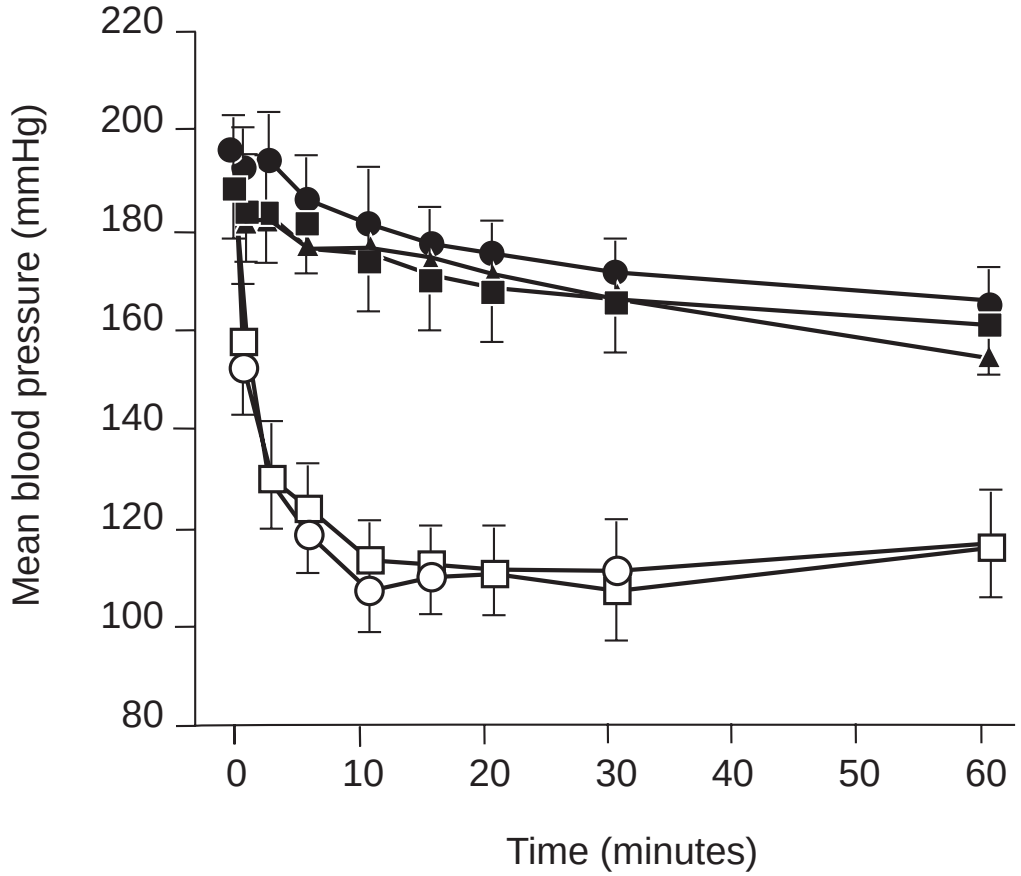
Table X

Binding of X and its Major Metabolites and Comparators to Human X_2 and X_3 Receptors

Compound	X_2 K_i1(nM)	X_2 K_i2(nM)	X_3 K_i1(nM)	X_3 K_i2(nM)
1	538	2730	691	4550
2	2699	1050	2.0	181
3	578	14.4	141	10400
4	20	100	10.7	7.9
5	2100	3.1	281	28
6	7.5	8.4	44	2.8
7	3.11	3.76	1.94	1.93

K_i1 and K_i2 represent the high and low affinity binding sites respectively (Data from Study Number).

Figure X: Blood Pressure Following Chronic Dosing With X to SHR[a]



Blood pressure following chronic dosing with X to SHR[a][ref]. Hypotensive effect of saline i.v. infusion over 5 min (s) compared to X, 3 mg/kg i.v. infusion to SHR pretreated twice daily with saline, 1 mL/kg p.o., for 7 (m) or 14 (p) days or X, 25 mg/kg p.o., for 7 (l) or 14 (n) days. Saline pretreated statistical significances: $p<0.05$, all other points after challenge $p<0.01$. Values represent mean ± s.e.m.

[a]SHR= spontaneous hypertensive rat (n=5 per group)

Table X

Model-independent pharmacokinetic parameters for X in mice following single oral doses at 2, 10 and 30 mg/kg [ref]

Parameter (units)	**Parameter value**					
Sex	**Males**			**Females**		
Dose (mg/kg)	2	10	30	2	10	30
C_{max} (ng/mL)	4.9	20.4	30.7	5.5	12.9	28.6
T_{max} (h)	0.8	0.4	0.3	0.4	0.5	0.3
AUC_{0-t} (ng.h/mL)	21.6	80.5	267	33.3	80	298
AUC_{0-inf} (ng.h/mL)	28.3	112	297	40.2	90	327

Pharmacokinetic parameters were determined in pooled plasma from three animals at each time

Table X: Excretion of radioactive material following single doses of [^{14}C]X to male mice [ref]

Dose (mg/kg)/ route		Percentage of administered dose		
		Urine*	Faeces	
2.8	i.v.	88.1 ± 7.4	5.5 ± 0.7	93.6 ± 6.9
8.8	p.o.	89.4 ± 4.7	6.9 ± 1.4	95.3 ± 3.4

Excretion was determined over 168 hours after dosing
Values are means ± S.D. (n= 5 for p.o. and 5 for i.v.)
* - includes radioactivity in cage wash (22.1% after p.o. and 21.7% after i.v.)
+ - includes radioactivity in the carcass

Table X: Concentrations of Radioactive Material in the Tissues of Male Rats After a Single Intravenous Dose of [^{14}C]X at 1.75 mg/kg [refs]

Tissue	Concentration (ng equiv.*/g)				
	1 h	6 h	24 h	48 h	72 h
Blood	105	96.6	2.34	2.34	3.65
Plasma	142	175	3.12	ND	ND
Adrenals	656	49.2	14.3	9.63	ND
Bone marrow	359	31.5	ND	ND	ND
Brain	116	9.37	ND	ND	ND
Eyes	124	28.9	4.69	ND	ND
Fat	490	44.0	10.2	6.25	5.47
Heart	105	26.6	ND	ND	ND
Kidneys	1280	651	21.6	13.3	9.63
Large intestine	570	2470	39.3	12.0	ND
Liver	875	380	133	87.7	64.6
Lungs	234	59.1	7.55	ND	ND

* - ng of X free base equivalent/g.
N= 5 animals/time point
ND - Not detected

Table X: Excretion of Radioactive Material Following Single Doses of [^{14}C]X to Male Rats [refs]

Dose (mg/kg)/ route		Percentage of administered dose			
		Urine	**Feces**	**Bile**	**Total**
1.75	i.v.	61.3 ± 9.3	30.3 ± 4.1	-	95.2 ± 5.0
1.75	p.o.	57.4 ± 3.8	37.0 ± 3.4	-	95.2 ± 1.5
2	p.o.	72.3 ± 0.8	26.9 ± 1.9	-	99.5 ± 1.1
20	p.o.	23.5 ± 6.3	0.5 ± 0.2	76.0 ± 5.9	100 ± 0.8
220	p.o.	67.1 ± 9.0	24.8 ± 5.0	-	93.3 ± 6.8

Excretion was determined over 168 h period in Wistar rats:Values are means ± S.D. (n=5); - not assayed; Total includes radioactivity in the carcass and cage washings.

Table X: Comparative Pharmacokinetic Data and Systemic Exposure to X Following Oral Administration to Mice, Rats, Dogs, and Patients [ref]

Species (formulation)	Dose (mg/kg/day)	Systemic (plasma) exposure		References
		C_{max} (ng/mL)	AUC (ng.h/mL)#	
Man (tablet)	0.48$	36.7	557	X
Mouse (solution)	8.8	68.9 (1.9)*	72.7 (0.2)*	Y
	21.9	267 (7.3)*	207 (0.5)*	
	43.8	430 (11.7)*	325 (0.7)*	
Rat (solution)	50	479 (13.0)*	1580 (2.8)*	Z
Dogs (solution)	1.5	5.58 (0.2)*	15.9 (<0.1)*	V
	5	24.8 (0.7)*	69.3 (0.1)*	
	15	184 (5.0)*	511 (0.9)*	

Data presented are for male and female animals and are after daily repeated oral administration (at the end of the 60-day mouse study, 14 day rat study, and 1 year dog study). Data for man are extrapolated from dose normalised data obtained in male and female patients following t.i.d regimen.

- AUC_{0-6} in the mouse, AUC_{0-t} in the rat and in the dog and dose normalised $AUC_{0-\tau}$ x 24 in man. $ - calculated from the total daily dose assuming a bodyweight of 50 kg for man. * - Numbers in parentheses represent ratios of exposure in animals to those in patients.

Table X: Incidence of Proliferative Interstitial (Leydig) Cell Lesions in Rats [ref]

	Dose Groups			
Lesion	**Control**	**3 mg/kg**	**30 mg/kg**	**100 mg/kg**
Hyperplasia (only)	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)
Adenoma (only)	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)
Adenoma + Hyperplasia	x/50 (%)	x/50 (%)	x/50(%)	x/50 (%)
Total*	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)

* Adenoma and/or Hyperplasia.

APPENDIX B: THE NONCLINICAL TABULATED SUMMARIES – TEMPLATES

2.6.3 Pharmacology
- 2.6.3.1 Pharmacology: Overview
- 2.6.3.2 Primary Pharmacodynamics*
- 2.6.3.3 Secondary Pharmacodynamics*
- 2.6.3.4 Safety Pharmacology
- 2.6.3.5 Pharmacodynamic Drug Interactions*

2.6.5 Pharmacokinetics
- 2.6.5.1 Pharmacokinetics: Overview
- 2.6.5.2 Analytical Methods and Validation Reports*
- 2.6.5.3 Pharmacokinetics: Absorption After a Single Dose
- 2.6.5.4 Pharmacokinetics: Absorption after Repeated Doses
- 2.6.5.5 Pharmacokinetics: Organ Distribution
- 2.6.5.6 Pharmacokinetics: Plasma Protein Binding
- 2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
- 2.6.5.8 Pharmacokinetics: Other Distribution Study
- 2.6.5.9 Pharmacokinetics: Metabolism In Vivo
- 2.6.5.10 Pharmacokinetics: Metabolism In Vitro
- 2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways
- 2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes
- 2.6.5.13 Pharmacokinetics: Excretion
- 2.6.5.14 Pharmacokinetics: Excretion into Bile
- 2.6.5.15 Pharmacokinetics: Drug-Drug Interactions
- 2.6.5.16 Pharmacokinetics: Other

2.6.7 Toxicology
- 2.6.7.1 Toxicology: Overview
- 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies
- 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data
- 2.6.7.4 Toxicology: Drug Substance
- 2.6.7.5 Single-Dose Toxicity
- 2.6.7.6 Repeat-Dose Toxicity: Non-pivotal Studies
- 2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies
- 2.6.7.8 Genotoxicity: In Vitro
- 2.6.7.9 Genotoxicity: In Vivo
- 2.6.7.10 Carcinogenicity
- 2.6.7.11 Reproductive and Developmental Toxicity: Non-pivotal Studies
- 2.6.7.12 Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)
- 2.6.7.13 Reproductive and Developmental Toxicity: Effects on Embryofetal Development (Pivotal)
- 2.6.7.14 Reproductive and Developmental Toxicity: Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)
- 2.6.7.15 Studies in Juvenile Animals[a]
- 2.6.7.16 Local Tolerance
- 2.6.7.17 Other Toxicity Studies

* : Tabulated Summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.

[a] : When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 2.6.7.15.

2.6.3.1 Pharmacology **Overview** **Test Article:** (1)

Type of Study	Test System	Method of Administration	Testing Facility	Study Number*(4)*	Location Vol.	Location Section
Primary Pharmacodynamics *(2)*					*(3)*	
Secondary Pharmacodynamics						
Safety Pharmacology						
Pharmacodynamic Drug Interactions						

Notes: *(1) International Nonproprietary Name (INN)*
(2) There should be one line for each pharmacology report, in the same order as the CTD. Reports that contain a GLP Compliance Statement should be identified in a footnote.
(3) The location of the Technical Report in the CTD should be indicated.
(4) Or Report Number (on all tables).

2.6.3.4 Safety Pharmacology*(1)* **Test Article:** *(2)*

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses[a] (mg/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number*(3)*

Notes: *(1) All safety pharmacology studies should be summarized.*
(2) International Nonproprietary Name (INN).
(3) Or Report Number (on all tables).

a - Single dose unless specified otherwise.

2.6.5.1 Pharmacokinetics **Overview** **Test Article:** *(1)*

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Section
Absorption *(2)*					*(3)*	
Distribution						
Metabolism						
Excretion						
Pharmacokinetic Drug Interactions						
Other						

Notes: *(1) International Nonproprietary Name (INN).*
(2) There should be one line for each pharmacokinetics report, in the same order as the CTD. Reports that contain a GLP Compliance Statement should be identified in a footnote.
(3) The location of the Technical Report in the CTD should be indicated.

2.6.5.3 Pharmacokinetics: Absorption After a Single Dose

Test Article: *(1)*

Location in CTD: Vol. Section
Study No.

Species	_____	_____	_____	_____	_____
Gender (M/F) / Number of animals	***(4)***				
Feeding condition					
Vehicle/Formulation					
Method of Administration					
Dose (mg/kg)					
Sample (whole blood, plasma, serum etc.)					
Analyte					
Assay ***(2)***					
PK parameters:					

Additional Information: ***(3)***

Notes: *(1) International Nonproprietary Name (INN).*
(2) For example, HPLC, LSC with ^{14}C-labeled compound.
(3) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
(4) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included.

2.6.5.4 Pharmacokinetics: Absorption after Repeated Doses **Test Article:**

[Data can be tabulated as in the format of 2.6.5.3 if applicable.]

Format A

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. Section
Study No.

Species:
Gender (M/F)/Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Radionuclide:
Specific Activity:
Sampling time:

	Concentration (unit)					
Tissues/organs	**T(1)**	**T(2)**	**T(3)**	**T(4)**	**T(5)**	**$t_{1/2?}$**

Additional information:

Alternate Format B

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article:

Location in CTD: Vol. Section
Study No.

Species:
Gender (M/F) / Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Radionuclide:
Specific Activity:
Analyte/Assay (unit):
Sampling time:

	C_t		Last time point				
Tissues/organs	**conc.**	**T/P[1)]**	**conc.**	**T/P[1)]**	**Time**	**AUC**	**$t_{1/2?}$**

Additional information:

[1)] **[Tissue]/[Plasma]**

2.6.5.6 Pharmacokinetics: Plasma Protein Binding **Test Article:**

Study system:
Target entity, Test system and method:

Species	Conc. tested	% Bound	Study No.	Location in CTD Vol.	Section

Additional Information:

2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals ***(1)***

Test Article: ***(2)***

Location in CTD: Vol. Section

Placental transfer

Study No.

Species:
Gestation day / Number of animals:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Analyte:
Assay:
Time (hr) _____ _____ _____ _____ _____
Concentration / Amount (% of dose)
Dam ***(3)*****:**
Fetus ***(3)*****:**

Additional Information:

Location in CTD: Vol. Section

Excretion into milk

Study No.

Species:
Lactating date / Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Analyte:
Assay:
Time [hr] _____ _____ _____ _____ _____
Concentration:
Milk:
Plasma:
Milk/plasma:
Neonates:

Additional Information:

Notes for Table 2.6.5.7

(1) Even if the data are obtained in reproduction toxicology studies, they should be presented in this table.
(2) International Nonproprietary Name (INN).

(3) The tissue sampled should be described (e.g., plasma for dams, fetal concentrations).

2.6.5.8 Pharmacokinetics: Other Distribution Study

Test Article:

2.6.5.9 Pharmacokinetics: Metabolism *In Vivo* **Test Article:**

Gender(M/F) / Number of animals:
Feeding condition:
Vehicle/Formulation:
Method of Administration:
Dose (mg/kg):
Radionuclide:
Specific Activity:

				% of Compound in Sample				Location in CTD	
Species	**Sample**	**Sampling Time or Period**	**% of Dose in Sample**	**Parent**	**M1**	**M2**	**Study No.**	**Vol**	**Section**
	Plasma								
	Urine								
	Bile								
	Feces								
	Plasma								
	Urine								
	Bile								
	Feces								
	Plasma								
	Urine								
	Bile								
	Feces								

Additional Information:

Note: *Human data should be included for comparison, if available.*

2.6.5.10 Pharmacokinetics: Metabolism In Vitro

Test Article:

Location in CTD: Vol. Section
Study No.

Study system:

Time	_____	_____	_____	_____	_____
Concentration:					
Compounds					
Parent					
M-1					
M-2					

Additional Information:

Note: Human data should be included for comparison, if available.

2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways **Test Article:**

(Illustrate possible metabolic map indicating species in which metabolic reactions occur.)

2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes

Test Article:

Location in CTD: Vol. Section
Study No.

Note: Nonclinical studies only.

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.5.13 Pharmacokinetics: Excretion **Test Article:** ***(1)***

Species	_____	_____	_____	_____
Gender (M/F) / Number of animals	*(3)*			
Feeding condition				
Vehicle/Formulation				
Method of Administration				
Dose (mg/kg)				
Analyte				
Assay				

Excretion route ***(4)***	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**
Time												
0 - T hr												

Study number
Location in CTD

Additional Information: ***(2)***

Notes: (1) International Nonproprietary Name (INN).
(2) For example, brief textual results, species differences, gender differences, dose dependency, or special comments.
(3) There should be one column for each study conducted. For comparison, representative information on humans at the maximum recommended dose should be included. May be combined with the Absorption Table, if appropriate.
(4) Other routes (e.g., biliary, respiratory) should be added, if performed.

2.6.5.14 Pharmacokinetics: Excretion into Bile ***Test Article:***

[Data can be tabulated as in the format of 2.6.5.13 if applicable.]

2.6.5.15 Pharmacokinetics: Drug-Drug Interactions

Test Article:

Location in CTD: Vol. Section
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.5.16 Pharmacokinetics: Other

Test Article:

Location in CTD: Vol. Section
Study No.

Type of study:

Method:

Tabulated results:

Additional Information:

2.6.7.1 Toxicology **Overview** **Test Article:** ***(1)***

Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dosing**	**Doses (mg/kg[a])**	**GLP Compliance**	**Testing Facility**	**Study Number**	**Location** Vol. Section
Single-Dose Toxicity	*(2)*							*(3)*
Repeat-Dose Toxicity								
Genotoxicity								
Carcinogenicity								
Reproductive and Developmental Toxicity								
Local Tolerance								
Other Toxicity Studies								

Notes: (1) International Nonproprietary Name (INN).
(2) There should be one line for each toxicology report, in the same order as the CTD.
(3) The location of the Technical Report in the CTD should be indicated.

a - Unless otherwise specified. For Repeat-Dose Toxicity, the highest the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

2.6.7.2 Toxicokinetics **Overview of Toxicokinetics Studies** **Test Article:** ***(1)***

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Study Number	Location Vol.	Location Section
(2)						*(3)*	

Notes: (1) International Nonproprietary Name (INN).
(2) There should be one line for each toxicokinetics report, in the same order as the CTD (Section 3, Toxicology).
(3) *The location of the Technical Report in the CTD should be indicated.*

2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** ***(1)***

(2)

Notes: (1) International Nonproprietary Name (INN).
(2) A one- to three-page summary (tables and/or figures) of steady-state toxicokinetic data should be prepared in a format that facilitates comparisons across species, including humans.

2.6.7.4 Toxicology **Drug Substance** **Test Article:** ***(1)***

Batch No.	**Purity (%)**	**Specified Impurities ( )**	**Study Number**	**Type of Study**
PROPOSED SPECIFICATION:				
(2)				*(3)*

Notes: *(1) International Nonproprietary Name (INN).*
(2) All batches used in the Toxicology studies should be listed, in approximate chronological order.
(3) The Toxicology studies in which each batch was used should be identified.

2.6.7.5 Single-Dose Toxicity ***(1)*** **Test Article:** *(2)*

Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Doses (mg/kg)**	**Gender and No. per Group**	**Observed Maximum Non-lethal Dose (mg/kg)**	**Approximate Lethal Dose (mg/kg)**	**Noteworthy Findings**	**Study Number**

Notes: (1) All single-dose toxicity studies should be summarized, in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual duration, infusion rate, or age of test subjects.
(2) International Nonproprietary Name (INN).

2.6.7.6 Repeat-Dose Toxicity **Non-Pivotal Studies** ***(1)*** **Test Article:** *(2)*

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	NOAEL[a] (mg/kg)	Noteworthy Findings	Study Number

Notes: *(1) All repeat-dose toxicity studies (including all range-finding toxicity studies), other than the definitive GLP studies specified by ICH Guideline M3, should be summarized, in the same order as the CTD. Footnotes should be used to indicate special features, such as unusual age of test subjects.*

(2) International Nonproprietary Name (INN).

_____

a - No Observed Adverse-Effect Level.

2.6.7.7 *(1)* Repeat-Dose Toxicity *(2)* **Report Title:** **Test Article:** (*3)*

Species/Strain: **Duration of Dosing:** **Study No.**
Initial Age: **Duration of Postdose:** **Location in CTD:** Vol. Section
Date of First Dose: **Method of Administration:**
Vehicle/Formulation: **GLP Compliance:**

Special Features:
No Observed Adverse-Effect Level:

Daily Dose (mg/kg)	0 (Control)							
Number of Animals	M:	F:	M:	F:	M:	F:	M:	F:
Toxicokinetics: AUC ( ) *(4)*	*(5)*							
Noteworthy Findings								
Died or Sacrificed Moribund								
Body Weight (%[a])								
Food Consumption (%[a])	*(5)*							
Water Consumption ( )	*(5)*							
Clinical Observations								
Ophthalmoscopy								
Electrocardiography								

\- No noteworthy findings. + Mild ++ Moderate +++ Marked *(6)*
(7) * - $p<0.05$ ** - $p<0.01$
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

Daily Dose (mg/kg)	0 (Control)							
Number of Animals	M:	F:	M:	F:	M:	F:	M:	F:
Hematology								
Serum Chemistry								
Urinalysis								
Organ Weights[a] (%)								
Gross Pathology								
Histopathology								
Additional Examinations								
Postdose Evaluation: Number Evaluated *(8)*								

\- No noteworthy findings.

(7) * - $p<0.05$ ** - $p<0.01$

a - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

Notes for Table 2.6.7.7

(1) The tables should be numbered consecutively: 2.6.7.7A, 2.6.7.7B, 2.6.7.7C etc.

(2) There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.

(3) International Nonproprietary Name (INN).

(4) Steady-state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If from a separate study, the Study Number should be given in a footnote.

(5) ONLY NOTEWORTHY FINDINGS SHOULD BE PRESENTED. If additional parameters (other than those in the Template) showed noteworthy changes, these should be added to the tables. In general, data at end of dosing period can be shown; however, if there were additional noteworthy findings at earlier timepoints, these should be included. Footnotes should be used as needed to provide additional information about the tests or the results.

(6) Or other scale, as appropriate.

(7) Methods of statistical analyses should be indicated.

(8) All parameters that still show drug-related changes should be listed. This section should be deleted if the study does not include a Postdose Evaluation.

(9) When appropriate, information on animals that were necropsied early should be presented separately.

2.6.7.8 *(1)* Genotoxicity: <u>In</u> <u>Vitro</u> **Report Title:** **Test Article:** *(2)*

Test for Induction of: **No. of Independent Assays:** **Study No.**
Strains: **No. of Replicate Cultures:** **Location in CTD:** Vol. Section
Metabolizing System: **No. of Cells Analyzed/Culture:**
Vehicles: **For Test Article:** **For Positive Controls:** **GLP Compliance:**
Treatment: **Date of Treatment:**
Cytotoxic Effects:
Genotoxic Effects:

Metabolic <u>Activation</u>	Test <u>Article</u>	Concentration or Dose Level <u>(*(3)*)</u>	_____	_____	_____	_____	_____
Without Activation							
		(4)					
With Activation							

Notes: *(1) The tables should be numbered consecutively: 2.6.7.8A, 2.6.7.8B, etc. Results of replicate assays should be shown on subsequent pages.*
(2) International Nonproprietary Name (INN).
(3) Units should be inserted.
(4) If precipitation is observed, this should be inserted in a footnote.
(5) Methods of statistical analyses should be indicated

(5) * - $p<0.05$ ** - $p<0.01$

2.6.7.9 *(1)* Genotoxicity: In Vivo **Report Title:** **Test Article:** *(2)*

Test for Induction of:
Species/Strain:
Age:
Cells Evaluated:
No. of Cells Analyzed/Animal:
Special Features:
Toxic/Cytotoxic Effects:
Genotoxic Effects:
Evidence of Exposure:

Treatment Schedule:
Sampling Time:
Method of Administration:
Vehicle/Formulation:

Study No.
Location in CTD: Vol. Section

GLP Compliance:
Date of Dosing:

Test Article	Dose (mg/kg)	No. of Animals	_____	_____	_____	_____

Notes: *(1) The tables should be numbered consecutively: 2.6.7.9A, 2.6.7.9B, etc.*
(2) International Nonproprietary Name (INN).
(3) Methods of statistical analysis should be indicated.

(3) * - $p<0.05$ ** - $p<0.01$).

2.6.7.10 *(1)* Carcinogenicity **Report Title:** **Test Article:** *(2)*

Species/Strain: **Duration of Dosing:** **Study No.**
Initial Age: **Method of Administration:** **Location in CTD:** Vol. Section
Date of First Dose: **Vehicle/Formulation:**
Treatment of Controls: **GLP Compliance:**

Basis for High-Dose Selection: *(3)*
Special Features:

Daily Dose (mg/kg)	0 (Control)							
Gender	M	F	M	F	M	F	M	F
Toxicokinetics: AUC ( ) *(4)*								
Number of Animals								
At Start								
Died/Sacrificed Moribund								
Terminal Sacrifice								
Survival (%)	*(5)*							
Body Weight (%[a])								
Food Consumption (%[a])								

(6) * - p<0.05 ** - p<0.01
a - At 6 months. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

Daily Dose (mg/kg)	(Control)		0 (Control)							
Number Evaluated	M:	F:	M:	F:	M:	F:	M:	F:	M:	F:
Number of Animals with Neoplastic Lesions: *(7)*										
Noteworthy Findings:										
Gross Pathology										
Histopathology - Non-Neoplastic Lesions										

\- No noteworthy findings.
* - p<0.05 ** - p<0.01

Notes for Table 2.6.7.10

(1) Tables should be numbered consecutively: 2.6.7.10A, 2.6.7.10B, , etc. There should be one table for each carcinogenicity study.

(2) International Nonproprietary Name (INN).

(3) From ICH Guideline S1C.

(4) Steady-state AUC, Cmax, Css, or other toxicokinetic information supporting the study. If the information is from a separate study, the Study Number should be given in a footnote.

(5) If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.

(6) Methods of statistical analysis should be indicated.

(7) Drug-related lesions should be listed first. Then other lesions should be listed by alphabetically ordered organs/tissues.

2.6.7.11 Reproductive and Developmental Toxicity **Non-Pivotal Studies** ***(1)*** **Test Article:** *(2)*

Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Dosing Period**	**Doses mg/kg**	**No. per Group**	**Noteworthy Findings**	**Study Number**

Notes: *(1)All reproduction toxicity studies (including all relevant range-finding studies) other than the definitive GLP studies specified by ICH Guideline M3 should be summarized, in the same order as the CTD. However, investigative studies should be summarized using a more detailed template.*

(2)International Nonproprietary Name (INN).

2.6.7.12 ***(1)*** **Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation** ***(3)*** **Report Title:** **Test Article:** *(2)*

Design similar to ICH 4.1.1? **Duration of Dosing:** M: **Study No.**
Species/Strain: **Day of Mating:** ***(8)*** F: **Location in CTD:** Vol. Section
Initial Age: **Day of C-Section:**
Date of First Dose: **Method of Administration:** **GLP Compliance:**
Special Features: **Vehicle/Formulation:**
No Observed Adverse-Effect Level:
F_0 Males:
F_0 Females:
F_1 Litters:

Daily Dose (mg/kg)	**0 (Control)**
Males Toxicokinetics: AUC ( ) *(4)*	
No. Evaluated	
No. Died or Sacrificed Moribund	
Clinical Observations	
Necropsy Observations	
Body Weight (%[a])	
Food Consumption (%[a])	
Mean No. Days Prior to Mating	
No. of Males that Mated	
No. of Fertile Males	*(5)*

-No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
(7) *- p<0.05 ** - p<0.01
a - After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

Daily Dose (mg/kg)	**0 (Control)**
Females Toxicokinetics: AUC ( ) *(4)*	
No. Evaluated	
No. Died or Sacrificed Moribund	
Clinical Observations	
Necropsy Observations	
Premating Body Weight (%[a])	
Gestation Body Weight (%[a])	
Premating Food Consumption (%[a])	
Gestation Food Consumption (%[a])	
Mean No. Estrous Cycles/14 days	
Mean No. Days Prior to Mating	
No. of Females Sperm-Positive	
No. of Pregnant Females	
No. Aborted or with Total Resorption of Litter	
Mean No. Corpora Lutea	
Mean No. Implantations	
Mean % Preimplantation Loss	
Mean No. Live Conceptuses	
Mean No. Resorptions	
No. Dead Conceptuses	
Mean % Postimplantation Loss	

-No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$
a - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

Notes for Tables 2.6.7.12, 2.6.7.13, and 2.6.7.14

(1) If there are multiple studies of this type, the tables should be numbered consecutively: 2.6.7.12A, 2.6.7.12B, 2.6.7.13A, 2.6.7.13B, etc.

(2) International Nonproprietary Name (INN).

(3) If a modified study design is used, tables should be modified accordingly.

(4) Steady-state AUC, Cmax, or other toxicokinetic information supporting the study. If the information is from a separate study, the Study Number should be given in a footnote.

(5) POSSIBLE PRESENTATIONS OF THE RESULTS ARE SHOWN IN THESE TEMPLATES. DATA PRESENTATION SHOULD BE FLEXIBLE AND APPROPRIATE ACCORDING TO OPTIMAL STATISTICAL ANALYSIS AND THE DESIGN OF THE STUDY. If additional parameters showed drug-related changes, these should be added to the tables. Footnotes should be used as needed to provide additional information about the tests or the results.

(6) Or other scale as appropriate.

(7) Methods of statistical analysis should be indicated.

(8) Day of mating should be indicated; e.g., Day 0 or Day 1

2.6.7.13 ***(1)*** **Reproductive and Developmental Toxicity - Effects on Embryofetal Development** ***(3)*** **Report Title:** **Test Article:** *(2)*

Design similar to ICH 4.1.3? **Duration of Dosing:** **Study No.**
Day of Mating: ***(8)***
Species/Strain: **Day of C-Section:** **Location in CTD:** Vol. Section
Initial Age: **Method of Administration:**
Date of First Dose: **Vehicle/Formulation:** **GLP Compliance:**
Special Features:
No Observed Adverse-Effect Level:
F_0 Females:
F_1 Litters:

Daily Dose (mg/kg)	**0 (Control)**
Dams/Does: Toxicokinetics: AUC **()** *(4)*	
No. Pregnant	
No. Died or Sacrificed Moribund	*(5)*
No. Aborted or with Total Resorption of Litter	
Clinical Observations	
Necropsy Observations	
Body Weight (%[a])	
Food Consumption (%[a])	
Mean No. Corpora Lutea	
Mean No. Implantations	
Mean % Preimplantation Loss	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)* G = Gestation day
(7) * - p<0.05 ** - p<0.01
a- At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

Daily Dose (mg/kg)	**0 (Control)**
Litters: No. Litters Evaluated	
No. Live Fetuses	
Mean No. Resorptions	
No. of Litters with Dead Fetuses	
Mean % Postimplantation Loss	
Mean Fetal Body Weight (g)	
Fetal Sex Ratios	
Fetal Anomalies:	
Gross External	
Visceral Anomalies	
Skeletal Anomalies	
Total Affected Fetuses (Litters)	

- No noteworthy findings.

* - $p<0.05$ ** - $p<0.01$

2.6.7.14 ***(1)*** **Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function** ***(3)*** **Report Title:** **Test Article:** *(2)*

Design similar to ICH 4.1.2? **Duration of Dosing:** **Study No.**
Day of Mating: ***(8)***

Species/Strain: **Method of Administration:** **Location in CTD:** Vol. Section
Initial Age **Vehicle/Formulation:**
Date of First Dose: **Litters Culled/Not Culled:** **GLP Compliance:**
Special Features:
No Observed Adverse-Effect Level:
F_0 Females:
F_1 Males:
F_1 Females:

Daily Dose (mg/kg)	**0 (Control)**
F_0 Females: Toxicokinetics: AUC ( ) *(4)*	
No. Pregnant	
No. Died or Sacrificed Moribund	
No. Aborted or with Total Res. of Litter	
Clinical Observations	
Necropsy Observations	*(5)*
Gestation Body Weight (%[a])	
Lactation Body Weight (%[a])	
Gestation Food Consumption (%[a])	
Lactation Food Consumption (%[a])	
Mean Duration of Gestation (days)	
Abnormal Parturition	

\- No noteworthy findings. + Mild ++Moderate +++Marked *(6)* G = Gestation day
(7) * - $p<0.05$ ** - $p<0.01$) L = Lactation day
a - At end of gestation or lactation. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

Daily Dose (mg/kg)		**0 (Control)**
F_1 Litters:	No. Litters Evaluated	
(Preweaning)	Mean No. of Implantations	
	Mean No. Pups/Litter	
	Mean No. Liveborn Pups/Litter	
	No. of Litters with Stillborn Pups	
	Postnatal Survival to Day 4	
	Postnatal Survival to Weaning	
	No. of Total Litter Losses	
	Change in Pup Body Weights[a] (g)	
	Pup Sex Ratios	
	Pup Clinical Signs	
	Pup Necropsy Obs.	
F_1 Males:	No. Evaluated Postweaning	
(Postweaning)	Per Litter	
	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Body-Weight Change[b] (g)	
	Food Consumption (%[c])	
	Preputial Separation	
	Sensory Function	
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Males that Mated	
	No. of Fertile Males	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$
a - From birth to weaning.
b - From weaning to mating.
c - At end of postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

Daily Dose (mg/kg)		**0 (Control)**
F_1 Females:	No. Evaluated Postweaning	
(Postweaning)	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Premating Body-Weight Change[a] (g)	
	Gestation Body-Weight Change (g)	
	Premating Food Consumption (%[b])	
	Gestation Food Consumption (%[b])	
	Mean Age of Vaginal Patency (days)	
	Sensory Function	
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Females Sperm-Positive	
	No. of Pregnant Females	
	Mean No. Corpora Lutea	
	Mean No. Implantations	
	Mean % Preimplantation Loss	
F_2 Litters:	Mean No. Live Conceptuses/Litter	
	Mean No. Resorptions	
	No. of Litter with Dead Conceptuses	
	No. Dead Conceptuses	
	Mean % Postimplantation Loss	
	Fetal Body Weights (g)	
	Fetal Sex Ratios (% males)	
	Fetal Anomalies	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*

*(7)** - $p<0.05$ ** - $p<0.01$

a - From weaning to mating

b - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

Daily Dose (mg/kg)		**0 (Control)**
F_1 Females:	No. Evaluated Postweaning	
(Postweaning)	No. Died or Sacrificed Moribund	
	Clinical Observations	
	Necropsy Observations	
	Premating Body-Weight Change[a] (g)	
	Gestation Body-Weight Change (g)	
	Premating Food Consumption (%[b])	
	Gestation Food Consumption (%[ab])	
	Mean Age of Vaginal Patency (days)	*Note: Alternate Format for Natural Parturition.*
	Sensory Function	
	Motor Activity	
	Learning and Memory	
	Mean No. Days Prior to Mating	
	No. of Females Sperm Positive	
	No. of Pregnant Females	
	Mean Duration of Gestation	
	Abnormal Parturition	
F_2 Litters:	No. Litters Evaluated	
	Mean No. of Implantations	
	Mean No. Pups/Litter	
	Mean No. Liveborn Pups/Litter	
	Mean No. Stillborn Pups/Litter	
	Postnatal Survival to Day 4	
	Postnatal Survival to Weaning	
	Change in Pup Body Weights[a] (g)	
	Pup Sex Ratios	
	Pup Clinical Signs	
	Pup Necropsy Obs	

- No noteworthy findings. + Mild ++Moderate +++Marked *(6)*
*(7)** - $p<0.05$ ** - $p<0.01$
a - From birth to mating.
b - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.16 Local Tolerance ***(1)*** **Test Article:** *(2)*

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number

Notes: *(1) All local-tolerance studies should be summarized.*
(2) International Nonproprietary Name (INN).

2.6.7.17 Other Toxicity Studies ***(1)*** **Test Article:** *(2)*

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number

Notes: *(1) All supplementary toxicity studies should be summarized.*
(2) International Nonproprietary Name (INN).

APPENDIX C: THE NONCLINICAL TABULALTED SUMMARIES - EXAMPLES

EXAMPLE

2.6.3.1 Pharmacology **Overview** **Test Article:** Curitol Sodium

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Section
Primary Pharmacodynamics						
Antiviral activity vs. VZV	Human embryonic lung fibroblasts	In vitro	Sponsor Inc.	95401	1	
Antiviral activity vs. VZV		In vitro	Sponsor Inc.	95402	1	
Antiviral activity vs. HSV	Clinical isolates	In vitro	Sponsor Inc.	95406	1	
Antiviral activity vs. CMV	Human embryonic lung fibroblasts	In vitro	Sponsor Inc.	95408	1	
Antiviral activity vs. VZV		Gavage	Sponsor Inc.	95411	1	
Antiviral activity vs. SVV	Human embryonic lung fibroblasts ICR mice African Green monkeys	Nasogastric Intubation	Sponsor Inc.	95420	1	
Secondary Pharmacodynamics						
Antimicrobial activity	Gram positive and gram negative bacteria; yeasts	In vitro	Sponsor Inc.	95602	1	
Safety Pharmacology						
Effects on central nervous system[a]	Mice, rats, rabbits, and cats	Gavage	Sponsor Inc.	95703	2	
Effects on cardiovascular system	Dogs	Gavage, i.v.	Sponsor Inc.	95706	2	
Pharmacodynamic Drug Interactions						
Interactions with anti-HIV activity of AZT	Human T lymphocytes	In vitro	Sponsor Inc.	95425	2	

a - Report contains a GLP Compliance Statement.

EXAMPLE

2.6.3.4 Safety Pharmacology **Test Article:** Curitol Sodium

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses[a] (mg/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
CNS	CD-1 Mice	Gavage	0, 10, 50, 250	10M	Slight prolongation of hexobarbital anesthesia (≥10 mg/kg). No analgesic, anticonvulsive, or cataleptic properties. No effects on coordination, traction, or spontaneous motility.	Yes	92201
Renal, GI, CNS, and Hemostasis	CD-1 Mice	Gavage	0, 10, 50, 250	6M	Slight increases in urinary excretion of sodium and potassium (≥50 mg/kg). No effects on GI transit time (charcoal meal), pupillary diameter, blood coagulation time, or urine volume.	No	92205
Cardiovascular	Mongrel Dogs	Intravenous	0, 3, 10, 30	3M	Dose-related transient decreases in blood pressure and increases in heart rate and respiratory rate (all doses). Minor ECG changes at 30 mg/kg. No effects on cardiac output, stroke volume, or total peripheral resistance.	Yes	92210

a - Single dose unless specified otherwise.

EXAMPLE

2.6.5.1 Pharmacokinetics **Overview** **Test Article:** Curitol Sodium

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol.	Location Section
Absorption						
Absorption and excretion	Rats	Gavage, i.v.	Sponsor Inc.	93302	1	
Absorption and excretion	Dogs	Gavage, i.v.	Sponsor Inc.	93304	1	
Absorption and excretion	Monkeys	Gavage, i.v.	Sponsor Inc.	93306	1	
Distribution						
Single-dose tissue distribution	Rats	Gavage	Sponsor Inc.	93307	1	
Repeat-dose tissue distribution	Rats	Gavage	Sponsor Inc.	93308	1	
Plasma protein binding	Mice, rats, dogs,	In vitro	Sponsor Inc.	93311	1	
Plasma protein binding	monkeys, Humans, rats, dogs	Tablets/Gavage/ Capsules	Sponsor Inc.	93312	1	
Metabolism						
Metabolites in blood, urine, and feces	Rats	Gavage	Sponsor Inc.	93402	1	
Metabolites in blood, urine, and feces	Dogs	Gavage	Sponsor Inc.	93407	1	
Excretion						
Absorption and excretion	Rats	Gavage, i.v.	Sponsor Inc.	93302	1	
Absorption and excretion	Dogs	Gavage, i.v.	Sponsor Inc.	93304	1	
Absorption and excretion	Monkeys	Gavage, i.v.	Sponsor Inc.	93306	1	
Pharmacokinetic Drug Interactions						
Interaction with AZT[a]	Rats	Gavage	Sponsor Inc.	94051	1	

a - Report contains a GLP Compliance Statement.

EXAMPLE

2.6.5.3 Pharmacokinetics: Absorption After a Single Dose

Test Article: Curitol Sodium
Location in CTD Volume 1, Section
Study number 95104

Species	**Mouse**	**Rat**	**Dog**	**Monkey**	**Human**
Gender (M/F) / Number of animals	4M	3M	4F	2M	6M
Feeding condition	Fed	Fasted	Fasted	Fed	Fasted
Vehicle/Formulation	Suspension 10% acacia	Suspension 10% acacia	Capsule	Suspension 10% acacia	Tablet
Method of Administration	Gavage	Gavage	Capsule	Gavage	Oral
Dose (mg/kg)	15	8	5	5	4 mg
Sample (e.g., whole blood, plasma, serum)	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte	TRA[a]	MM-180801	MM-180801	MM-180801	MM-180801
Assay	LSC	HPLC	HPLC	HPLC	HPLC
PK parameters:					
Tmax (hr)	4.0	1.0	3.3	1.0	6.8
Cmax (ng/ml or ng-eq/ml)	2,260	609	172	72	8.2
AUC (ng or ng-eq x hr/ml)	15,201	2,579	1,923	582	135
(Time for calculation – hr)	(0-72)	(0-24)	(0.5-48)	(0-12)	(0-24)
T 1/2 (hr)	10.6	3.3	9.2	3.2	30.9
(Time for calculation – hr)	(7-48)	(1-24)	(24-96)	(1-12)	(24-120)

Additional Information:

A single oral dose was well absorbed in mice, rats, dogs, and monkeys.

In a study examining the concentration of compound in the portal vein and inferior vena cava, 30 minutes after a dose to rats, the concentration of compound was approximately 15-fold higher in the portal circulation compared to systemic circulation. This result indicated extensive metabolism and/or biliary secretion of compound in the rat.

a - Total radioactivity, ^{14}C

EXAMPLE

Format A

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: Curitol Sodium
Location in CTD: Vol.21, Section
Study No. 95207

Species: Rat
Gender (M/F)/Number of animals: 3M/each time point
Feeding condition: Fasted
Vehicle/Formulation: Solution/Water
Method of Administration: Oral Gavage
Dose (mg/kg): 10
Radionuclide: ^{14}C
Specific Activity: $2x10^5$ Bq/mg
Sampling time: 0.25, 0.5, 2, 6, 24, 96, and 192 hr

	Concentration (mcg/mL)					
Tissues/organs	**0.25**	**0.5**	**2**	**6**	**24**	**$t_{1/2}$**
Blood	9.2	3.7	1.8	0.9	0.1	
Plasma	16.5	7.1	3.2	1.6	0.2	
Brain	0.3	0.3	0.2	0.1	nd	
Lung	9.6	14.1	7.3	2.9	0.1	
Liver	73.0	54.5	19.9	12.4	3.2	
Kidney	9.6	13.2	4.9	3.8	0.6	
Testis	0.3	0.5	0.6	0.5	0.1	
Muscle	1.0	1.2	0.8	0.3	nd	

Additional information:

Heart, thymus, adrenal, spleen, stomach, intestine,….are examined but not shown.

nd = Not detected.

EXAMPLE

Alternate Format B

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: Curitol Sodium
Location in CTD: Vol. 21, Section
Study No. 95207

Species: Rat
Gender (M/F) / Number of animals: 3M/each time point
Feeding condition: Fed
Vehicle/Formulation: Solution/Saline
Method of Administration: Intravenous
Dose (mg/kg): 1
Radionuclide: Non-labeled compound
Specific Activity: -
Analyte/Assay: Unchanged compound (mcg/mL)/HPLC
Sampling time: 10 min, 1, 4, 8, 24, 48, 96, and 168 hr

	C_{1hr}		Last time point				
Tissues/organs	**conc.**	**T/P[1)]**	**conc.**	**T/P[1)]**	**Time**	**AUC**	**$t_{1/2}$**
Heart	1.4	0.08	0.44	22	48	57.3	37.3
Liver	4.5	6	1.85	92.5	48	290	51.7
Kidney	2.8	0.20	1.07	53.5	48	126	36.3
Spleen	6.5	8.6	3.5	175	48	410	46.9

Additional information:

[1)] **[Tissue]/[Plasma]**

EXAMPLE

2.6.5.6 Pharmacokinetics: Protein Binding **Test Article:** Curitol Sodium

Study system: In vitro
Target entity, Test system and method: Plasma, Ultrafiltration

Species	Conc. tested	% Bound	Study No.	Location in CTD Vol.	Location in CTD Section
Rat	1 - 100uM	82.1 - 85.4	95301	21	
Dog	1 - 100uM	83.5 - 88.2	95301	21	
Human	1 - 100uM	75.2 - 79.4	96-103-03	45	

Additional Information:

2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals

Test Article: Curitol Sodium
Location in CTD: Vol. 22, Section
Study No. 95702

Placental transfer
Species: Rat
Gestation day / Number of animals: 14 and 19 days gestation/3 animals at each time point
Vehicle/Formulation: Solution/Water
Method of Administration: Oral gavage
Dose (mg/kg): 5
Analyte: Total radioactivity, ^{14}C
Assay: LSC

Time (hr.)	**14 days/30 min.**	**14 days/24 hr.**	**19 days/30 min.**	**19 days/24 hr.**
Concentration/Amount (% of dose)				
Maternal plasma	12.4	0.32	13.9	0.32
Placenta	3.8	0.14	3.3	0.32
Amniotic fluid	0.07	0.04	0.04	0.13
Whole fetus	0.54	0.03	0.39	0.10

Additional Information:
Maternal blood, liver, kidney, ovary, uterus were also examined but not shown.

Location in CTD: Vol. 22 Section
Study No. 95703

Excretion into milk
Species: Rat
Lactating date / Number of animals: day 7/3
Feeding condition: Fed
Vehicle/Formulation: Solution/Water
Method of Administration: Oral gavage
Dose (mg/kg): 5
Analyte: Total radioactivity, ^{14}C
Assay: LSC

Time [hr]	**1**	**2**	**4**	**6**	**8**	**24**
Concentration:						
Milk:	0.6	0.8	1.0	1.1	1.3	0.4
Plasma:	1.5	1.4	1.2	0.8	0.6	0.1
Milk/plasma:	0.40	0.57	0.83	1.4	2.2	4.0
Neonates						

Additional Information:

EXAMPLE

2.6.5.9 Pharmacokinetics: Metabolism *In Vivo* **Test Article:** Curitol Sodium

Gender (M/F)/Number of animals: **Rats:** 4M **Dogs:** 3F **Humans:** 8M
Feeding condition: Fed
Vehicle/Formulation: **Rats:** Solution/water **Dogs:** Capsules **Humans:** 75-mg tablets
Method of Administration: **Rats:** Gavage* **Dogs:** Oral Capsule* **Humans:** Oral Tablet
Dose (mg/kg): **Rats:** 5 mg/kg **Dogs:** 5 mg/kg **Humans:** 75 mg
Radionuclide: ^{14}C
Specific Activity: 2 x 10^5 Bq/mg

				% of Compound in Sample				Location in CTD	
Species	**Sample**	**Sampling Time or Period**	**% of Dose in Sample**	**Parent**	**M1**	**M2**	**Study Number**	**Vol.**	**Section**
Rats	Plasma	0.5 hr	-	87.2	6.1	3.4	*95076*	26	
	Urine	0-24 hr	2.1	0.6	n.d.	0.2			
	Bile	0-4 hr	28.0	15.5	7.2	5.1			
	Feces	-	-	-	-	-			
Dogs	Plasma	0.5 hr	-	92.8	n.d.	7.2	95082	26	
	Urine	0-24 hr	6.6	6.4	n.d.	n.d.			
	Bile	0-4 hr	32.0	28.5	2.8	n.d.			
	Feces	-	-	-	-	-			
Humans	Plasma	1 hr	-	87.5	trace	12.5	CD-102	42	
	Urine	0-24 hr	5.5	2.4	2.9	n.d.			
	Bile	-	-	-	-	-			
	Feces	-	-	-	-	-			

Additional Information

* - Intraduodenal administration for collection of bile.
n.d. - None detected.

EXAMPLE

2.6.5.13 Pharmacokinetics: Excretion **Test Article:** Curitol Sodium

Species	Rat			Rat			Dog			Dog		
Gender (M/F) / Number of animals	4M			4M			3M			3M		
Feeding condition	Fasted			Fasted			Fasted			Fasted		
Vehicle/Formulation	Solution Water			Solution Saline			Capsule			Solution Saline		
Method of Administration	Oral			Intravenous			Oral			Intravenous		
Dose (mg/kg)	10			5			10			5		
Analyte	TRA[a]			TRA[a]			TRA[a]			TRA[a]		
Assay	LSC			LSC			LSC			LSC		
Excretion route	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total**
Time												
0 - 24 hr	26	57	83	22	63	85	20	29	49	23	42	65
0 - 48 hr	30	65	95	27	69	96	25	65	90	28	78	96
0 - 72 hr	31	65	97	28	70	98	26	73	99	29	72	101
0 - 96 hr	31	67	98	29	70	99	26	74	100	29	73	102

Study number	95102	95156
Location in CTD	Volume 20, Section	Volume 20, Section

Additional Information:

a - Total radioactivity; percent recovery, ^{14}C

EXAMPLE

2.6.5.14 Pharmacokinetics: Excretion into Bile **Test Article:** Curitol Sodium

Species	**Rat**			**Rat**		
Gender (M/F) / Number of animals	4M			4M		
Feeding condition	Fasted			Fasted		
Vehicle/Formulation	Solution			Solution		
	Water			Saline		
Method of Administration	Oral			Intravenous		
Dose (mg/kg)	10			5		
Analyte	TRA[a]			TRA[a]		
Assay	LSC			LSC		
Excretion route	**Bile**	**Urine**	**Total**	**Bile**	**Urine**	**Total**
Time						
0 - 2 hr	37	-	37	75	-	75
0 - 4 hr	50	-	50	82	-	82
0 - 8 hr	62	-	62	86	-	86
0 - 24 hr	79	9	86	87	11	98
0 - 48 hr	83	10	93	88	11	99

Study number 95106
Location in CTD Volume 20, Section

a - Total radioactivity; percent recovery, ^{14}C

EXAMPLE

2.6.7.1 Toxicology **Overview** **Test Article:** Curitol Sodium

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg[a])	GLP Compliance	Testing Facility	Study Number	Location Vol.	Location Section
Single-Dose Toxicity	CD-1 Mice	Gavage	-	0, 1000, 2000, 5000	Yes	Sponsor Inc.	96046	1	
		Intravenous	-	0, 100, 250, 500	Yes	CRO Co.	96047	1	
	Wistar Rats	Gavage	-	0, 1000, 2000, 5000	Yes	Sponsor Inc.	96050	1	
		Intravenous	-	0, 100, 250, 500	Yes	CRO Co.	96051	1	
Repeat-Dose Toxicity	CD-1 Mice	Diet	3 Months	0, 62.5, 250, 1000, 4000, 7000	Yes	CRO Co.	94018	2	
	Wistar Rats	Diet	2 Weeks	0, 1000, 2000, 4000	No	Sponsor Inc.	94019	3	
		Gavage	2 Weeks	0, 500, 1000, 2000	No	Sponsor Inc.	94007	3	
		Gavage	3 Months	0, 200, 600, 1800	Yes	Sponsor Inc.	94214	4	
		Gavage	6 Months	0, 100, 300, 900	Yes	Sponsor Inc.	95001	5	
	Beagle Dogs	Capsules	1 Month	0, 10, 40, 100	Yes	Sponsor Inc.	94020	6	
		Capsules	9 Months	0, 5, 20, 50	Yes	Sponsor Inc.	96041	7	
	Cynomolgus Monkeys	Gavage	5 Days	0, 500, 1000	No	CRO Co.	94008	8	
Genotoxicity	S. typhimurium and E. coli	In Vitro	-	0, 500, 1000, 2500, and/or 5000 mcg/plate	Yes	Sponsor Inc.	96718	9	
	Human Lymphocytes	In Vitro	-	0, 2.5, 5, 10, 20, and 40 mcg/ml	Yes	CRO Co.	97634	9	
	Wistar Rats	Gavage	3 Days	0, 1000, 2000	Yes	Sponsor Inc.	96037	9	

a - Unless otherwise specified. For Single-Dose Toxicity and Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined.

(Continued)

EXAMPLE

2.6.7.1 Toxicology **Overview (Continued)** **Test Article:** Curitol Sodium

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number	Location Vol.	Location Section
Carcinogenicity	CD-1 Mice	Diet	21 Months	0, 0, 25, 100, 400	Yes	CRO Co.	95012	10	
	Wistar Rats	Gavage	24 Months	0, 0, 25, 100, 400	Yes	Sponsor Inc.	95013	12	
Reproduction Toxicity	Wistar Rats	Gavage	a	0, 5, 30, 180	Yes	CRO Co.	96208	14	
	Wistar Rats	Gavage	F: G6 - G15[b]	0, 10, 100, 1000	Yes	Sponsor Inc.	94211	15	
	NZW Rabbits	Gavage	F: G6 - G18[b]	0, 1, 5, 25	Yes	CRO Co.	97028	16	
	Wistar Rats	Gavage	F: G6 - L21[b]	0, 7.5, 75, 750	Yes	Sponsor Inc.	95201	17	
Local Tolerance	NZW Rabbits	Dermal	1 Hour	0, 15 mg	No	Sponsor Inc.	95015	18	
Other Toxicity Studies									
Antigenicity	Guinea Pigs	Subcutaneous	Weekly for 3 weeks	0, 5 mg	No	CRO Co.	97012	18	
Impurities	Wistar Rats	Gavage	2 Weeks	0, 1000, 2000	Yes	Sponsor Inc.	97025	18	

_____

a - Males: 4 weeks prior to mating. Females - 2 weeks prior to mating through Gestation Day 7.
b - G = Gestation Day L = Lactation Day

EXAMPLE

2.6.7.2 Toxicokinetics **Overview of Toxicokinetics Studies** **Test Article:** Curitol Sodium

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Study Number	Location Vol.	Location Section
Three-month range-finding study	Mice	Diet	62.5, 250, 1000, 4000, 7000	Yes	94018	2	
Two-week toxicity study	Rats	Gavage	500, 1000, 2000	No	94007	3	
Six-month toxicity study	Rats	Gavage	100, 300, 900	Yes	95001	5	
One-month toxicity study	Dogs	Capsules	10, 40, 100	Yes	94020	6	
Nine-month toxicity study	Dogs	Capsules	5, 20, 50	Yes	96041	7	
Carcinogenicity study	Mice	Diet	25, 100, 400	Yes	95012	10	
Carcinogenicity study	Rats	Gavage	25, 100, 400	Yes	95013	12	
Toxicokinetics study	Rabbits	Gavage	1, 5, 25	No	97231	16	

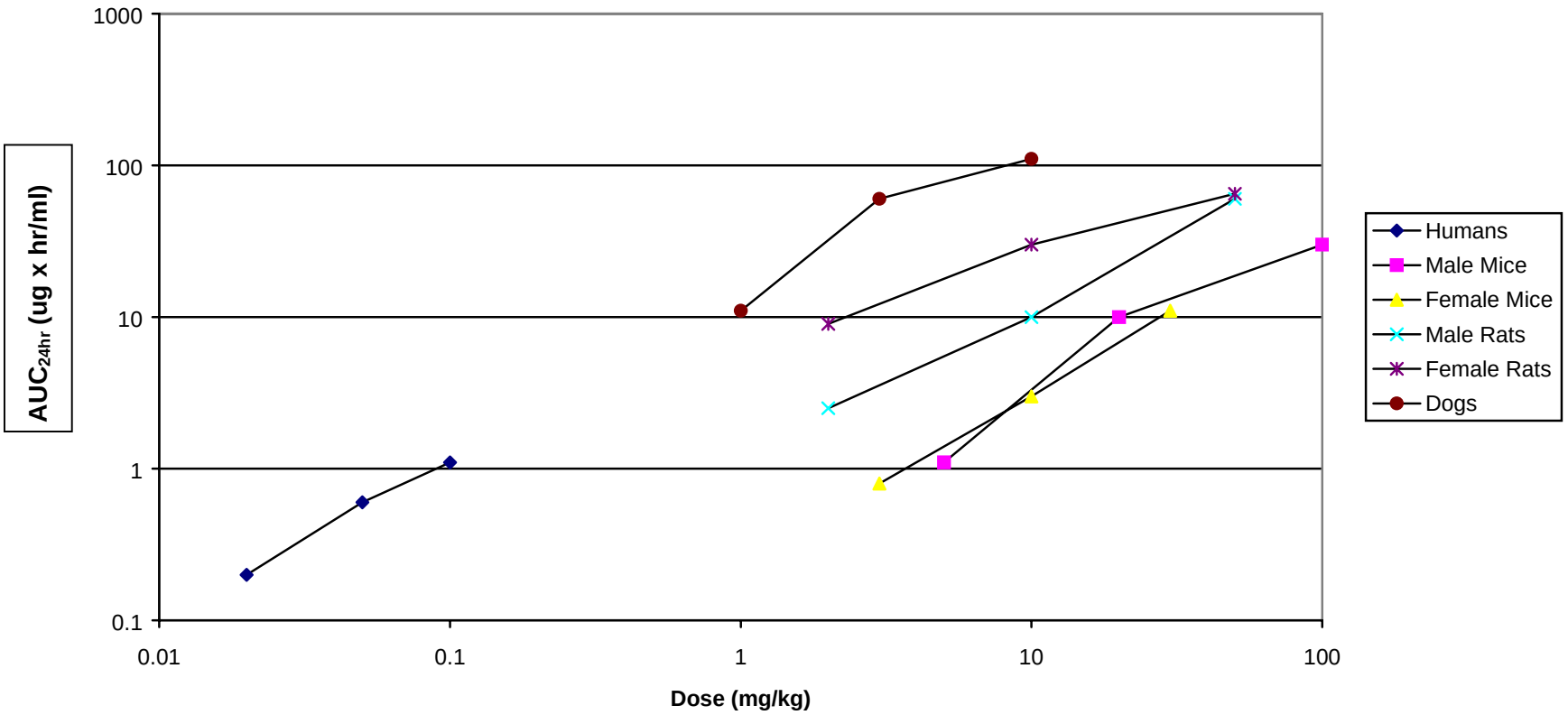
2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** Curitol Sodium

	Steady-State AUC (mcg-hr/ml)						
Daily Dose	**Mice[a]**		**Rats[b]**			**Female**	
(mg/kg)	**M**	**F**	**M**	**F**	**Dogs[c]**	**Rabbits[b]**	**Humans[f]**
1						9	3
5					3	25	
10					4		
20					10		
25	10	12	6	8		273	
40					10		
50					12		
62.5	35	40					
100	40	48	25[d], 20[e]	27[d], 22[e]	40		
250	120	135					
300			68	72			
400	815	570	90	85			
500			125	120			
900			200	190			
1000	2,103	1,870	250	240			
2000			327	321			
4000	4,975	3,987					
7000	8,241	7,680					

_____
a - In diet.
b - By gavage.
c - In capsules. Males and females combined.
d - Six-month toxicity study.
e - Carcinogenicity study.
f - Protocol 147-007.

EXAMPLE

2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article : Curitol Sodium**



Steady-state AUC_{24hr} values of unchanged MM-180801 in humans after repeated oral administration of 1, 2.5, and 5 mg OD, in comparison with those in mice in the carcinogenicity study, rats in the 6-month toxicity study, and dogs in the 9-month toxicity study.

EXAMPLE

2.6.7.4 Toxicology **Drug Substance** **Test Article:** Curitol Sodium

Batch No.	Purity (%)	Specified Impurities[a]			Study Number	Type of Study
		A	B	C		
PROPOSED SPECIFICATION:	>95	≤ 0.1	≤ 0.2	≤ 0.3	-	-
LN125	98.2	0.1	0.1	0.2	94007	Two-Week Oral Range-Finding Study in Rats
					94008	Five-Day Oral Range-Finding Study in Monkeys
					96718	Ames Test
94NA103	99.1	0.2	0.1	0.2	96046	Single-Dose Oral Study in Mice
					96050	Single-Dose Oral Study in Rats
					94214	Three-Month Oral Study in Rats
					94020	One-Month Oral Study in Dogs
					97634	Human Lymphocytes Assay In Vitro
95NA215	97.3	0.1	0.3	0.1	96047	Single-Dose Intravenous Study in Mice
					96051	Single-Dose Intravenous Study in Rats
					96037	Micronucleus Test in Rats
					94211	Embryo-fetal Development Study in Rats
					97028	Embryo-fetal Development Study in Rabbits
95NB003	94.6	0.2	0.3	0.4	94019	Two-Week Palatability Study in Rats
					97012	Antigenicity Study in Hamsters
96NB101	99.0	0.4	0.1	0.0	94018	Three-Month Dietary Range-Finding Study in Mice
					95001	Six-Month Oral Study in Rats
					95002	One-Year Oral Study in Dogs
					95012	Dietary Carcinogenicity Study in Mice
					95013	Oral Carcinogenicity Study in Rats
					96208	Fertility and Early Embryonic Development Study in Rats
					95015	Dermal Irritation Study in Rabbits

a - Area percent.

EXAMPLE

2.6.7.5 Single-Dose Toxicity **Test Article:** Curitol Sodium

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Gender and No. per Group	Observed Maximum Nonlethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Study Number
CD-1 Mice	Gavage (Water)	0, 1000, 2000, 5000	10M 10F	≥5000 ≥5000	>5000	≥2000: Transient body weight losses. 5000: Decreased activity, convulsions, collapse.	96046
	Intravenous (Saline)	0, 100, 250, 500	10M 10F	250 250	>250 <500	≥250: Body-weight losses. 500: 3M and 2F died.	96047
Wistar Rats	Gavage (CMC Suspension)	0, 1000, 2000, 5000	5M 5F	2000 ≥5000	>2000 <5000	≥2000: Transient body weight losses; inactivity; chromorhinorrhea. 5000: 2M died.	96050
	Intravenous (5% Dextrose)	0, 100, 250, 500	5M 5F	250 ≥500	>250 <500	≥250: Body weight losses in males. 500: 3M died.	96051

EXAMPLE

2.6.7.6 Repeat-Dose Toxicity **Non-Pivotal Studies** **Test Article:** Curitol Sodium

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	NOAEL[a] (mg/kg)	Noteworthy Findings	Study Number
CD-1 Mice	Diet	3 Months	0, 62.5, 250, 1000, 4000, and 7000	10M, 10F	M:4000 F: 1000	≥4000: Lower body weights; gastric erosions/ulcers in some mice. 7000: 4M and 6F died/ sacrificed; lower body weights; single-cell necrosis in liver.	94018
Wistar Rats	Diet	2 Weeks	0, 1000, 2000, and 4000	5M, 5F	1000	≥2000: Lower body weights. 4000: 2M and 1F sacrificed moribund.	94019
	Gavage (Water)	2 Weeks	0, 500, 1000, and 2000	5M, 5F	1000	2000: Lower body weights; single-cell necrosis in liver.	94007
Beagle Dogs	Gavage (CMC Suspension)	5 Days	0, 500, and 1000	1M, 1F	<500	≥500: Weight losses, inappetence.	94008

a - No Observed Adverse-Effect Level.

2.6.7.7A Repeat-Dose Toxicity **Report Title:** MM-180801: Three-Month Oral Toxicity Study in Rats **Test Article:** Curitol Sodium

Species/Strain: Wistar Rats
Initial Age: 5 Weeks
Date of First Dose: 15 Jan 94

Duration of Dosing: 3 Months
Duration of Postdose: 1 Month
Method of Administration: Gavage
Vehicle/Formulation: Aqueous Solution

Study No. 94214
Location in CTD: Vol. 4, Section

GLP Compliance: Yes

Special Features: None
No Observed Adverse-ffect Level: 200 mg/kg

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
Number of Animals	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
Toxicokinetics: AUC (mcg-hr/ml):								
Day 1	-	-	30	28	130	125	328	302
Day 28	-	-	52	47	145	140	400	380
Day 90	-	-	50	51	160	148	511	475
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%[a])	394 g	244 g	0	-1	-10*	-11*	-25**	-45**
Food Consumption (%[a])	20.4 g	17.2 g	0	-1	-1	-8*	-30**	-50**
Clinical Observations								
Hyperactivity	-	-	-	-	-	+	-	++
Chromorhinorrhea, reddish-stained coat, white feces	-	-	-	-	-	-	++	++
Emaciated, piloerection, stilted gait	-	-	-	-	-	-	-	++
Ophthalmoscopy	-	-	-	-	-	-	-	-

- No noteworthy findings. + Mild ++ Moderate +++ Marked
Dunnett's Test: *- p<0.05 ** - p<0.01
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

2.6.7.7A Repeat-Dose Toxicity **Study No. 94214 (Continued)**

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
Number of Animals	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
Hematology								
Hemoglobin (g/dl)	15.8	15.0	15.7	14.9	15.8	14.6	14.0*	13.1*
Erythrocyte Count ($x10^6/mm^3$)	8.1	-	7.9	-	8.1	-	7.4*	-
MCH	-	22	-	21	-	22	-	19*
MCHC	-	34	-	34	-	34	-	30*
Platelet Count ($x10^3/mm^3$)	846	799	825	814	914	856	931*	911*
Serum Chemistry								
Creatinine (IU/L)	0.7	0.7	0.7	0.7	0.7	0.7	1.1*	1.1*
Proteins g/dl)	-	6.7	-	6.6	-	6.6	-	5.0**
Cholesterol (mg/dl)	96	-	86	-	90	-	105*	-
ALT (IU/L)	67	56	60*	52	55*	47*	53*	58
AST (IU/L)	88	92	96	90	87*	84*	85*	93
Bilirubin (mg/dl)	0.18	0.20	0.17	0.20	0.18	0.20	0.22**	0.26**
Calcium (mEq/L)	-	10.7	-	10.8	-	10.8	-	9.8**
Phosphorus (mEq/L)	9.3	-	9.3	-	9.3	-	8.2*	-
Urinalysis								
Protein Conc. (mg/dl)	260	49	102	34	123	54	126*	22*
pH	7.5	-	7.5	-	7.2	-	6.3**	-
Glucose (mg/dl)	-	0	-	0	-	20	-	98**
Urine Volume (ml)	-	18	-	18	-	16	-	12*

- No noteworthy findings.

Dunnett's Test: *- $p<0.05$ **- $p<0.01$

(Continued)

2.6.7.7A Repeat-Dose Toxicity **Study No. 94214 (Continued)**

Daily Dose (mg/kg)	0 (Control)		200		600		1800	
Number of Animals	M:30	F:30	M:20	F:20	M:20	F:20	M:30	F:30
Organ Weights[b] (%)								
Kidney	3.01 g	1.75 g	0	+5*	+1	+8**	+12**	+20**
Liver	15.9 g	8.01 g	0	+1	+10*	+12*	+12*	+20**
Gross Pathology								
Number examined	20	20	20	20	20	20	20	20
Kidneys: Pallor	0	0	0	0	0	5	1	2
Glandular Stomach: Discoloration	0	0	0	0	0	1	1	4
Histopathology								
Number examined	20	20	20	20	20	20	20	20
Kidneys: Tubular dilatation	0	0	0	0	0	6	3	4
Mild	0	0	0	0	0	6	1	0
Moderate	0	0	0	0	0	0	2	4
Glandular Stomach: Erosions	0	0	0	0	0	2	2	9
Additional Examinations	-	-	-	-	-	-	-	-
Postdose Evaluation:								
Number Evaluated	10	10	0	0	0	0	10	10
Body Weight[a] (%)	422 g	265 g	-1	-2	-3	-4	-10*	-20**
Kidney Weight[b] (%)	3.24 g	1.81 g	0	-1	-1	0	+8*	+10

- No noteworthy findings.

Dunnett's Test: * - $p<0.05$ **- $p<0.01$

a - At end of postdose recovery period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

EXAMPLE #2

2.6.7.7B Repeat-Dose Toxicity **Report Title:** MM-180801: One-Month Oral Toxicity Study in Dogs **Test Article:** Curitol Sodium

Species/Strain: Beagle Dogs
Initial Age: 5-6 Months
Date of First Dose: 2 Feb 94

Duration of Dosing: 1 Month
Duration of Postdose: None
Method of Administration: Oral
Vehicle/Formulation: Gelatin Capsules

Study No. 94020
Location in CTD: Vol. 6, Section

GLP Compliance: Yes

Special Features: Hepatic enzyme induction evaluated at termination.
No Observed Adverse-Effect Level: 10 mg/kg

Daily Dose (mg/kg)	0 (Control)		10		40		100	
Number of Animals	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
Toxicokinetics: AUC (mcg-hr/ml):								
Day 1	-	-	5	6	10	12	40	48
Day 28	-	-	4	5	8	11	35	45
Noteworthy Findings								
No. Died or Sacrificed Moribund								
Body Weight (%[a])	0	0	0	0	0	0	0	0
Clinical Observations:	9.8 kg	9.2 kg	0	0	-1	-19**	0	-18**
Hypoactivity (after dosing)								
Ophthalmoscopy	-	-	-	-	-	-	+	++
Electrocardiography	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-
ALT (IU/L): Week 2	22	25	24	27	21	24	48*	69**
Week 4	25	27	26	25	23	25	54*	84**

- No noteworthy findings. + Mild ++ Moderate +++ Marked
Dunnett's Test: * - $p<0.05$ ** - $p<0.01$
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

2.6.7.7B Repeat-Dose Toxicity **Study No. 94020 (Continued)**

Daily Dose (mg/kg)	0 (Control)		10		40		100	
Number of Animals	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
Organ Weights[a] (%)								
Liver	339 g	337 g	+1	-1	+17**	+16**	+23**	+21**
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology								
Number Examined	3	3	3	3	3	3	3	3
Liver: Centrilobular hypertrophy	0	0	0	0	0	0	2	3
Additional Examinations								
Hepatic Enzyme Induction	-	-	-	-	-	-	-	-

- No noteworthy findings.

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$

a - Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

EXAMPLE #1

2.6.7.8A Genotoxicity: In Vitro **Report Title:** MM-180801: Ames Reverse Mutation Study in Salmonella and E. Coli **Test Article:** Curitol Sodium

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 2 **Study No.** 96669
Strains: S. typhimurium and E. coli **No. of Replicate Cultures:** 3 **Location in CTD:** Vol. 10, Section
Metabolizing System: Aroclor-induced rat liver S9**,** 7.1% **No. of Cells Analyzed/Culture:** -
Vehicles: **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes
Treatment: Plate incorporation for 48 hr. **Date of Treatment:** Feb. 1996
Cytotoxic Effects: None.
Genotoxic Effects: None.

Metabolic Activation	Test Article	Dose Level (mcg/plate)	Assay #1 Revertant Colony Counts (Mean ±SD)				
			TA 98	TA 100	TA 1535	TA 1537	WP2 uvrA
Without Activation	DMSO	100 mcl/plate	24 ± 9	129 ± 4	15 ± 4	4 ± 2	17 ± 3
	MM-180801	312.5	24 ± 6	128 ± 11	12 ± 4	4 ± 2	14 ± 2
		625	32 ± 9	153 ± 9	9 ± 2	8 ± 2	17 ± 5
		1250	30 ± 4	152 ± 12	9 ± 3	9 ± 2	18 ± 4
		2500	27 ± 5	140 ± 6	9 ± 3	5 ± 1	19 ± 1
		5000[a]	30 ± 3	137 ± 21	15 ± 1	7 ± 2	13 ±4
	2-Nitrofluorene	2	696				
	Sodium azide	1		542	468		
	9-Aminoacridine	100				515	
	MMS	2.5 mcl/plate					573
With Activation	DMSO	100 mcl/plate	27 ± 6	161 ± 12	12 ± 5	5 ± 1	21 ± 8
	MM-180801	312.5	31 ± 4	142 ± 8	12 ± 5	4 ± 2	17 ± 3
		625	30 ± 1	156 ± 15	17 ± 2	9 ± 5	23 3
		1250	33 ± 2	153 ± 13	13 ± 3	8 ± 2	18 ± 3
		2500	35 ± 8	160 ± 4	10 ± 2	8 ± 2	19 ± 5
		5000[a]	31 ± 4	153 ± 5	9 ± 4	7 ± 1	17 ±4
	2-Aminoanthracene	2.5	1552	1487	214	61	
		10					366

a - Precipitation.

EXAMPLE #2

2.6.7.8B Genotoxicity: In Vitro **Report Title:** MM-180801: Cytogenetics Study in Primary Human Lymphocytes **Test Article:** Curitol Sodium

Test for Induction of: Chromosome aberrations **No. of Independent Assays:** 1 **Study No.** 96668
Strains: Primary human lymphocytes **No. of Replicate Cultures:** 2 **Location in CTD:** Vol. 10, Section
Metabolizing System: Aroclor-induced rat liver S9**,** 5% **No. of Cells Analyzed/Culture:** 100
Vehicles: **Test Article:** DMSO **Positive Controls:** DMSO **GLP Compliance:** Yes
Treatment: Continuous treatment for 24-hr without S9; pulse treatment 5 hr and recovery time 24-hr with and without S9. **Date of Treatment:** Aug. 1996
Cytotoxic Effects: Dose-related decreases in mitotic indices.
Genotoxic Effects: Chromosome aberrations without S9 at 10 and 20 µg/ml, and with S9 at 50 and 200 µg/ml.

Metabolic Activation	Test Article	Concentration (mcg/ml)	Cytotoxicity[a] (% of control)	Aberrant Cells Mean %	Abs/Cell	*Total polyploid cells*
Without Activation	DMSO	-	100	2.0	0.02	4
	MM-180801	2.5	78	3.0	0.03	3
		5	59	4.0	0.05	4
		10	36	16.5**	0.20	2
		20	32	35.0**	0.55	3
	Mitomycin	0.10	52	38.5**	0.64	5
With Activation	DMSO	-	100	4.0	0.04	3
	MM-180801	2.5	91	4.5	0.05	3
		10	88	4.5	0.05	2
		50	80	9.5*	0.10	4
		200	43	34.0**	0.66	3
	Cyclophosphamide	4	68	36.5**	0.63	6

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$
a - Based on mitotic indices.

EXAMPLE #1

2.6.7.9A Genotoxicity: In Vivo **Report Title:** MM-180801: Oral Micronucleus Study in Rats **Test Article:** Curitol Solution

Test for Induction of: Bone marrow micronuclei
Species/Strain: Wistar Rats
Age: 5 Weeks
Cells Evaluated: Polychromatic erythrocytes
No. of Cells Analyzed/Animal: 2000
Special Features: None.

Treatment Schedule: Three daily doses.
Sampling Time: 24 hr after last dose.
Method of Administration: Gavage.
Vehicle/Formulation: Aqueous solution.

Study No: 96683
Location in CTD: Vol. 10, Section

GLP Compliance: Yes
Date of Dosing: July 1996

Toxic/Cytotoxic Effects: At 2000 mg/kg, clinical signs, two deaths, and decreases in bone marrow PCEs.
Genotoxic Effects: None.
Evidence of Exposure: Overt toxicity at 2000 mg/kg.

Test Article	Dose (mg/kg)	No. of Animals	Mean % PCEs (±SD)	Mean % MN-PCEs (±SD)
Vehicle	0	5M	52 ± 1.9	0.20 ± 0.12
MM-180801	2	5M	54 ± 3.7	0.25 ± 0.16
	20	5M	49 ± 3.1	0.20 ± 0.07
	200	5M	50 ± 2.1	0.26 ± 0.08
	2000	3M	31 ± 2.5	0.12 ± 0.03
Cyclophosphamide	7	5M	51 ± 2.3	2.49 ± 0.30**

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$

EXAMPLE #2

2.6.7.9B Genotoxicity: In Vivo **Report Title:** MM-180801: Oral DNA Repair Study in Rats **Test Article:** Curitol Solution

Test for Induction of: Unscheduled DNA synthesis
Species/Strain: Wistar Rats
Age: 5 Weeks
Cells Evaluated: Hepatocytes.
No. of Cells Analyzed/Animal: 100
Special Features: None.
Toxic/Cytotoxic Effects: None.
Genotoxic Effects: None.
Evidence of Exposure: Toxicokinetics - See Study No. 94007, Two-Week Oral Toxicity Study in Rats.

Treatment Schedule: Single dose.
Sampling Time: 2 and 16 hr.
Method of Administration: Gavage.
Vehicle/Formulation: Aqueous solution.

Study No: 51970
Location in CTD: Vol. 11, Section

GLP Compliance: Yes
Date of Dosing: Jan. 1997

Test Article	Dose (mg/kg)	No. of Animals	Time hrs.	Nuclear Mean ± SD	Cytoplasm Mean ± SD	NG Mean ± SD	% IR Mean ± SD	NGIR Mean ± SD
Vehicle	0	3M	16	3.5 ± 0.2	7.3 ± 0.3	-3.8 ± 0.4	0 ± 0	-
MM-180801	2	3M	2	3.0 ± 1.1	5.5 ± 1.4	-2.6 ± 0.4	0 ± 0	-
	2	3M	16	4.1 ± 0.5	6.5 ± 0.8	-2.4 ± 0.2	0 ± 0	-
	20	3M	2	3.9 ± 0.2	6.9 ± 0.3	-3.0 ± 0.1	1 ± 0	5.7 ± 0.4
	20	3M	16	3.6 ± 0.3	6.3 ± 0.4	-2.7 ± 0.2	0 ± 0	-
	200	3M	2	4.2 ± 0.2	7.5 ± 0.3	-3.4 ± 0.2	0 ± 0	-
	200	3M	16	3.1 ± 0.3	5.3 ± 0.3	-2.2 ± 0.1	0 ± 0	-
	2000	3M	2	4.8 ± 0.4	8.2 ± 0.7	-3.4 ± 0.4	0 ± 0	-
	2000	3M	16	2.7 ± 0.1	4.8 0.3	-2.1 ± 0.3	0 ± 0	-
DMN	10	3M	2	10.7 ± 3.0	5.8 ± 1.0	4.9 ± 2.1	41 ±15	11.4 ± 0.4

Nuclear = Nuclear grain count; the number of grains over the nucleus.
Cytoplasm = Cytoplasmic grain count; the highest grain count from 2 nuclear-sized areas adjacent to the nucleus.
NG = Net grains/nucleus; the nuclear count minus the cytoplasmic count.
% IR = Percentage of cells with at least 5 NG.
NGIR = Average net grains/nucleus of cells in repair.

EXAMPLE

2.6.7.10 Carcinogenicity **Report Title:** MM-180801: Dietary Carcinogenicity Study in Mice **Test Article:** Curitol Sodium

Species/Strain: CD-1 Mice
Initial Age: 6 Weeks
Date of First Dose: 20 Sep 95

Duration of Dosing: 21 months
Method of Administration: Diet
Vehicle/Formulation: In Diet
Treatment of Controls: Drug-Free Diet

Study No. 95012
Location in CTD: Vol. 4, Section

GLP Compliance: Yes

Basis for High-Dose Selection: Toxicity-based endpoint.
Special Features: 12 additional males and 12 additional females per drug-treated group bled at 6 months for toxicokinetic monitoring and then removed from the study.

Daily Dose (mg/kg)	0 (Control)		25		100		400	
Gender	M	F	M	F	M	F	M	F
Toxicokinetics:								
AUC on Day 28 (mcg-hr/ml[a])	-	-	10	12	40	48	815	570
Css on Day 180 (mcg/ml)	-	-	0.4	0.5	1.7	0.3	34	24
Number of Animals:								
At Start	60	60	60[c]	60	60	60	60	60
Died/Sacrificed Moribund	16	16	15	13	18	20	27	25
Terminal Sacrifice	44	44	44[c]	47	42	40	33	35
Survival (%)	67	73	75	80	71	68	56	59
Body Weight (%[b])	33g	31g	0	0	-7*	0	-13**	-19**
Food consumption (%[b])	6g/day	5g/day	0	0	-9*	-8*	-17**	-15**

Dunnett's Test: * - $p<0.05$ ** - $p<0.01$

a - From Study No. 95013.

b - At 6 months. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)

c - One missing mouse could not be evaluated.

(Continued)

2.6.7.10 Carcinogenicity **Study No. 95012 (Continued)**

Daily Dose (mg/kg)	0 (Control)		25		100		400	
Number Evaluated	M: 60	F: 60	M: 59	F: 60	M: 60	F: 60	M: 60	F: 60
Number of Animals with Neoplastic Lesions:								
Skin: Hemangioma	0	1	1	0	6[b]	1	13[b]	0
Hemangiosarcoma	1	3	2	2	9	11	18[a]	24[a]
Adrenal: Adrenocortical adenoma	4	1	2	0	4	3	3	1
Adrenocortical adenocarcinoma	0	0	0	0	0	1	0	0
Adenoma + Adenocarcinoma	4	1	2	0	4	3	3	1
Pheochromocytoma	0	0	0	0	1	1	0	1
Bone: Osteochondrosarcoma	0	1	0	1	0	0	0	0
Osteoma	0	1	0	0	0	0	0	0
Epididymis: Sarcoma, undifferentiated	0	0	1	0	0	0	1	0
Gallbladder: Adenoma	0	0	1	0	0	0	0	0
Harderian gland: Adenoma	4	2	3	1	3	4	3	1
Kidney: Renal cell adenoma	1	2	0	0	2	0	0	0
Liver: Hepatocellular adenoma	3	1	4	2	3	1	4	1
Hepatocellular carcinoma	2	1	1	2	3	1	0	1
Hepatocellular adenoma + carcinoma	3	2	4	3	5	2	4	1
Lung: Alveolar/bronchiolar adenoma	13	10	11	11	14	7	13	4
Alveolar/bronchiolar carcinoma	4	0	1	1	2	2	1	1
Adenoma + carcinoma	15	10	11	12	15	9	13	5

a - Trend analysis, $p<0.005$
b - Trend analysis, $p<0.025$

(Continued)

Daily Dose (mg/kg)	0 (Control)		25		100		400	
Number Evaluated	M: 60	F: 60	M: 59	F: 60	M: 60	F: 60	M: 60	F: 60
Mediastinum: Sarcoma, undifferentiated								
Oviduct: Adenoma	0	1	0	0	0	1	0	0
Pancreas: Islet cell adenoma		1		1		0		0
Peritoneum: Osteosarcoma	1	0	0	0	0	0	0	0
Seminal vesicle: Adenoma	1	0	0	0	1	0	0	1
Stomach: Osteochondrosarcoma	0		1		0		0	
Thymus: Thymoma	0	0	0	1	0	0	0	0
Thyroid: Follicular cell adenoma	0	1	0	0	0	0	0	0
Uterus: Papillary cystadenoma	0	1	0	0	0	1	0	0
Whole animal: Lymphosarcoma		1		0		2		0
Whole animal: Histiocytic sarcoma	6	13	4	11	3	12	5	11
	1	0	0	0	0	1	0	0
Noteworthy Findings:								
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology - Non-Neoplastic Lesions								
Liver: Hepatocellular hypertrophy	4	2	3	2	4	1	40**	45**
Testes: Hypospermatogenesis	1		2		15*		30**	

\- No noteworthy findings.
Fisher Exact Test: * - p<0.05 ** - p<0.01

EXAMPLE

2.6.7.11 Reproductive and Developmental Toxicity **Non-Pivotal Studies** **Test Article:** Curitol Sodium

Species/ Strain	**Method of Administration (Vehicle/ Formulation)**	**Dosing Period**	**Doses mg/kg**	**No. per Group**	**Noteworthy Findings**	**Study Number**
Wistar Rats	Gavage (Water)	G6 through G15	0, 500, 1000, 2000	8 Pregnant Females	≥1000: Deaths; weight losses; decreased food consumption; clinical signs; resorptions.	94201
NZW Rabbits	Gavage (CMC Suspension)	13 Days	0, 5,15, 45	6 Nonpregnant Females	≥15: Decreased weight gain and food consumption. 45: Four does died.	97020

G – Gestation day

EXAMPLE

2.6.7.12 Reproductive and Developmental Toxicity Fertility and Early Embryonic Development to Implantation

Report Title: MM-180801: Oral Study of Effects on Fertility and Early Embryonic Development in Rats

Test Article: Curitol Sodium

Design similar to ICH 4.1.1? Yes
Species/Strain: Wistar Rats
Initial Age: 10 Weeks

Duration of Dosing: M: 4 weeks prior to mating
F: 2 weeks prior to mating, through day 7 of gestation
Day of Mating: Day 0
Day of C-Section: Day 16 of gestation
Method of Administration: Gavage
Vehicle/Formulation: Aqueous solution.

Study No. 97072
Location in CTD: Vol. 6, Section

Date of First Dose: 3 Mar 97
Special Features: None
No Observed Adverse-Effect Level:
F_0 Males: 100 mg/kg
F_0 Females: 100 mg/kg
F_1 Litters: 1000 mg/kg

GLP Compliance: Yes

Daily Dose (mg/kg)		**0 (Control)**	**10**	**100**	**1000**
Males	Toxicokinetics: AUC[b] (mcg-hr/ml)	-	1.8	25	320
	No. Evaluated	22	22	22	22
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations:				
	Salivation	-	-	+	++
	Necropsy Observations	-	-	-	-
	Body Weight (%[a])	452 g	0	0	-12*
	Mean No. Days Prior to Mating	2.7	2.5	2.3	2.8
	No. of Males that Mated	22	21	22	22
	No. of Fertile Males	21	21	21	21

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - $p<0.05$ ** - $p<0.01$
a -After 4 weeks of dosing. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
b -From Study No. 94220.

(Continued)

Daily Dose (mg/kg)		**0 (Control)**	**10**	**100**	**1000**
Females	Toxicokinetics: AUC[b] (mcg-hr/ml)	-	2.1	27	310
	No. Evaluated	22	22	22	22
	No. Died or Sacrificed Moribund	0	1	0	0
	Clinical Observations				
	Salivation	-	-	-	+
	Necropsy Observations	-	-	-	-
	Premating Body Weight (%[a])	175 g	0	0	-5*
	Gestation Body Weight (%[a])	225 g	0	0	-12**
	Premating Food Consumption (%[a])	14 g	0	0	-6*
	Gestation Food Consumption (%[a])	15 g	0	0	-15**
	Mean No. Estrous Cycles/14 days	3.9	3.8	3.8	3.9
	Mean No. Days Prior to Mating	2.1	2.3	2.5	2.2
	No. of Females Sperm-Positive	21	22	22	21
	No. of Pregnant Females	21	21	22	20
	Mean No. Corpora Lutea	15.9	15.8	16.8	15.3
	Mean No. Implantations	14.5	14.0	15.3	13.8
	Mean % Preimplantation Loss	8.8	11.4	8.9	9.8
	Mean No. Live Conceptuses	13.3	13.3	14.3	12.8
	Mean No. Resorptions	1.2	0.7	1.0	1.0
	No. Dead Conceptuses	0	0	0	0
	Mean % Postimplantation Loss	8.3	5.0	6.5	7.2

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - $p<0.05$ ** - $p<0.01$

a - At end of premating or gestation period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b - From Study No. 94220.

2.6.7.13 Reproductive and Developmental Toxicity - Effects on Embryo-fetal Development

Report Title: MM-180801: Oral Study of Effects on **Test Article:** Curitol Sodium Embryofetal Development in Rabbits

Design similar to ICH 4.1.3? Yes
Day of Mating: Day 0
Species/Strain: NZW Rabbits
Initial Age: 5 months
Date of First Dose: 7 Aug 97
Special Features: None.
No Observed Adverse-Effect Level:
F_0 Females: 1 mg/kg
F_1 Litters: 5 mg/kg

Duration of Dosing: G6-G18
Day of C-Section: G29
Method of Administration: Gavage
Vehicle/Formulation: Aqueous Solution

Study No. 97028
Location in CTD: Vol. 6, Section
GLP Compliance: Yes

Daily Dose (mg/kg)		**0 (Control)**	**1**	**5**	**25**
Dams/Does:	Toxicokinetics: AUC[b] (mcg-hr/ml)	-	2.6	31	345
	No. Pregnant	20	19	20	20
	No. Died or Sacrificed Moribund	0	1	1	0
	No. Aborted or with Total Resorption of Litter	0	0	0	3
	Clinical Observations	-	-	-	++
	Necropsy Observations	-	-	-	-
	Body Weight (%[a])	3.2 kg	0	-15*	-20**
	Food Consumption (%[a])	60 g/day	0	-9*	-16**
	Mean No. Corpora Lutea	9.4	9.3	9.4	10.4
	Mean No. Implantations	7.9	8.1	9.1	9.4
	Mean % Preimplantation Loss	15.8	13.1	4.0	8.9

\- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day
Dunnett's Test * - $p<0.05$ ** - $p<0.01$
a - At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
b - From Study No. 97231.

(Continued)

Daily Dose (mg/kg)		**0 (Control)**	**1**	**5**	**25**
Litters:	No. Litters Evaluated	18	16	17	18
	No. Live Fetuses	140	126	148	86*
	Mean No. Resorptions	0.2	0.3	0.4	4.7**
	No. Dead Fetuses	1	0	0	0
	Mean % Postimplantation Loss	4.3	2.8	5.4	49.0**
	Mean Fetal Body Weight (g)	44.82	42.44	42.14	42.39
	Fetal Sex Ratios (% males)	46.3	57.7	57.4	52.8
	Fetal Anomalies:				
	Gross External				
	Lower jaw: Short				
	No. Fetuses (%)	0	0	0	7 (8.0)*
	No. Litters (%)	0	0	0	5 (27.8)**
	Visceral Anomalies				
	Tongue: Absent				
	No. Fetuses (%)	0	0	0	6 (6.9)*
	No. Litters (%)	0	0	0	6 (33.3)**
	Skeletal Anomalies				
	Mandible: Cleft				
	No. Fetuses (%)	0	0	0	10 (11.5)**
	No. Litters (%)	0	0	0	8 (44.4)**
	Ribs: Cervical				
	No. Fetuses (%)	2 (1.4)	0	1 (0.7)	0
	No. Litters (%)	1 (5.6)	0	1 (5.9)	0
	Sternebrae: Misshapen				
	No. Fetuses (%)	2 (1.4)	1 (0.8)	0	1 (1.2)
	No. Litters (%)	2 (11.1)	1 (6.3)	0	1 (5.6)
	Total Affected Fetuses (Litters)	2 (2)	1 (1)	0	15 (10)

- No noteworthy findings.

Fisher Exact Test * - $p<0.05$ ** - $p<0.01$

2.6.7.14 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function

Report Title: MM-180801: Oral Study of Effects on Pre- and Postnatal Development in Rats

Test Article: Curitol Sodium

Design similar to ICH 4.1.2? Yes

Duration of Dosing: G6 - L21

Day of Mating: Day 0

Study No. 95201

Species/Strain: Wistar Rats

Method of Administration: Gavage

Location in CTD: Vol. 10, Section

Initial Age: 9-10 Weeks

Vehicle/Formulation: Water

Date of First Dose: 8 Oct 95

Litters Culled/Not Culled: Culled to 4/sex/litter

GLP Compliance: Yes

Special Features: None

No Observed Adverse-Effect Level:

F_0 Females: 7.5 mg/kg

F_1 Males: 75 mg/kg

F_1 Females: 75 mg/kg

Daily Dose (mg/kg)		**0 (Control)**	**7.5**	**75**	**750**
F_0 Females:	Toxicokinetics: AUC[b] (mcg-hr/ml)	-	2.4	21	150
	No. Pregnant	23	21	22	23
	No. Died or Sacrificed Moribund	0	0	0	8
	Clinical Observations	-	-	++	+++
	Necropsy Observations	-	-	-	-
	Gestation Body Weight (%[a])	225 g	0	0	-25**
	Lactation Body Weight (%[a])	210 g	0	0	0
	Gestation Food Consumption (%[a])	15 g	0	0	-12*
	Lactation Food Consumption (%[a])	16 g	0	0	0
	Mean Duration of Gestation (days)	22.1	22.2	22.1	23.5[+]
	Abnormal Parturition	-	-	-	-

- No noteworthy findings. + Mild ++Moderate +++Marked G = Gestation day
Dunnett's Test * - p<0.05 ** - p<0.01 L = Lactation day
Kruskal-Wallis with Dunn's procedure + - p<0.05

a -At end of gestation or lactation. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b -From Study No. 97227

(Continued)

2.6.7.14 Reproductive and Developmental Toxicity **Study No. 95201**

(Continued)

Daily Dose (mg/kg)		**0 (Control)**	**7.5**	**75**	**750**
F_1 Litters:	No. Litters Evaluated	23	21	22	15
(Preweaning)	Mean No. Pups/Litter	13.6	13.8	14.9	11.2^{++}
	Mean No. Liveborn Pups/Litter	13.5	13.8	14.6	9.4^{++}
	Mean No. Stillborn Pups/Litter	0.1	0.0	0.3	1.8^{+}
	Postnatal Survival to Day 4	-	-	-	-
	Postnatal Survival to Weaning	-	-	-	-
	Change in Pup Body Weights[a] (g)	60	58	62	53*
	Pup Sex Ratios (% males)	51	53	49	51
	Pup Clinical Signs	-	-	-	-
	Pup Necropsy Obs.	-	-	-	-
F_1 Males:	No. Evaluated Postweaning	23	21	22	15
(Postweaning)	No. Died or Sacrificed Moribund	-	-	-	-
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight Change[b] (g)	200	195	195	186*
	Food Consumption (%[b])	15 g	0	0	-11*
	Preputial Separation	-	-	-	-
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	2.4	3.3	2.9	3.5
	No. of Males that Mated	23	21	21	23
	No. of Fertile Males	23	21	19	20

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - $p<0.05$ ** - $p<0.01$
Kruskal-Wallis with Dunn's procedure + - $p<0.05$ ++ - $p<0.01$

a - From birth to weaning.

b - From weaning to mating. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). (Continued)

Daily Dose (mg/kg)		**0 (Control)**	**7.5**	**75**	**750**
F_1 Females:	No. Evaluated Postweaning	23	21	22	23
(Postweaning)	No. Died or Sacrificed Moribund	0	1	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Premating Body-Weight Change[a] (g)	226	230	235	196*
	Gestation Body-Weight Change (g)	153	160	144	158
	Premating Food Consumption (%[b])	15 g	0	0	-13*
	Gestation Food Consumption (%[b])	16 g	0	0	0
	Mean Age of Vaginal Patency (days)	-	-	-	-
	Sensory Function	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and Memory	-	-	-	-
	Mean No. Days Prior to Mating	2.4	3.3	3.1	3.5
	No. of Females Sperm Positive	23	21	21	23
	No. of Pregnant Females	23	21	20	21
	Mean No. Corpora Lutea	16.4	16.2	15.8	15.5
	Mean No. Implantations	15.8	15.2	14.4	14.9
	Mean % Preimplantation Loss	3.8	6.3	12.3	3.7
F_2 Litters:	Mean No. Live Conceptuses/Litter	15.0	14.9	13.6	14.4
	Mean No. Resorptions	0.8	0.3	0.8	0.5
	No. Dead Conceptuses	0	0	0	0
	Mean % Postimplantation Loss	5.1	2.2	5.2	3.4
	Fetal Body Weights (g)	3.69	3.65	3.75	3.81
	Fetal Sex Ratios (% males)	53	49	54	54
	Fetal Anomalies	-	-	-	-

- No noteworthy findings. + Mild ++Moderate +++Marked
Dunnett's Test * - $p<0.05$ ** - $p<0.01$
a - From weaning to mating.
b - During postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

(Continued)

EXAMPLE

2.67.17 Other Toxicity Studies **Test Article:** Curitol Sodium

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Antigenicity						
Guinea Pigs	Subcutaneous	Weekly for 3 weeks; challenge 1 week later.	0, 5 mg	5M, 5F	Mildly positive delayed hypersensitivity reaction. No evidence of passive cutaneous anaphylaxis or systemic anaphylaxis.	97012
Impurities						
WISTAR Rats	Gavage	2 Weeks	0, 1000, 2000	10M, 10F	MM-180801 fortified with 2% of the Z-isomer impurity; toxicologic effects comparable to MM-180801 without impurity.	97025

Module 2.7
Clinical Summary

Preamble

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; 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 CTD 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

Detailed Guidance on Sections of the Clinical Summary

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.7.1.1 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.

2.7.1.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutic studies should generally be provided (see 2.7.1.4 Appendix), 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.

2.7.1.3 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 2.7.1.4 Appendix) 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 intrasubject variability for each formulation in a comparative BA study.

2.7.1.4 Appendix

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 2.7.1.1 and 2.7.1.2 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.

2.7.2 Summary of Clinical Pharmacology Studies

2.7.2.1 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 sections 2.7.1, 2.7.3 and 2.7.4 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, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD relationships[2]. 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, choice of the intrinsic or extrinsic factors that were studied, 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.

2.7.2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided (see 2.7.2.5 Appendix), 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 2.7.3 or 2.7.4 as appropriate and referenced, but not summarised, here.

[2] In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively.

2.7.2.3 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 and the intrinsic and extrinsic factors 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., paediatric 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 that may be due to extrinsic or intrinsic factors.
- 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 Section 2.7.3.4.
- major inconsistencies in the human biomaterial, PK, or PD database.
- PK studies that were performed to determine whether foreign clinical data could be extrapolated to the new region (see ICH E5). The result of the studies and analysis of the similarity of the PK data between regions or races should be summarised in this section. Such studies that use PD biomarkers (but do not evaluate clinical efficacy) may similarly be summarised here. An independent subsection can be created to summarise these kinds of data.

2.7.2.4 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 the Summary of Clinical Safety (section 2.7.4).

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 2.7.3. 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, 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 Section 2.7.3, 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.

2.7.2.5 Appendix

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 2.7.2.1 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.

2.7.3 Summary of Clinical Efficacy

A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labelled 2.7.3 pneumonia, 2.7.3 URI, etc.

2.7.3.1 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 Section 2.7.4, 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.

2.7.3.2 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 the section 2.7.3.6 Appendix), 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.

Narratives of any bridging studies using clinical endpoints, i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be included in this section. An analysis of the results of such studies, together with other information (e.g., PK and PD data) that addresses the ability to extrapolate the efficacy and safety results of foreign studies, should be performed if necessary. The conclusions of such an analysis should be noted at the start of Section 2.7.3.3.2, Comparison of Efficacy Results of All Studies, and the full report of the analysis should be provided in Module 5.

2.7.3.3 Comparison and Analyses of Results Across Studies

Using text, figures, and tables as appropriate (see the section 2.7.3.6 Appendix), the subsections of 2.7.3.3 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 Module 5, Section 5.3.5.3.

This section should also cross-reference important evidence from section 2.7.2, 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., paediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships.

2.7.3.3.1 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.

2.7.3.3.2 Comparison of Efficacy Results of all Studies

The results of any bridging studies using clinical endpoints, i.e., certain studies used to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be summarised in this section. An analysis of the similarity of efficacy in subjects between regions, as well as any other information that may support extrapolation of the efficacy data to the new region, should be summarised here. An independent subsection can be created to summarize these kinds of data.

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 (section 5.3.5.3 of Module 5).

2.7.3.3.3 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) and of other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) 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 paediatric 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 Module 5, with the results of those analyses reported here.

2.7.3.4 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 Section 2.7.2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in Section 2.7.2.2, 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 Section 2.7.2 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).

2.7.3.5 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 section 2.7.4).

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.

2.7.3.6 Appendix

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 2.7.3 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 2.7.3.1 Description of Clinical Efficacy and Safety Studies
Table 2.7.3.2 Results of Efficacy Studies

2.7.4 Summary of Clinical Safety

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

The display of safety-related data can be considered at three levels (ICH E3):

- The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database.
- The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarised.
- Serious adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and their occurrence should be summarised. These events should be examined for frequency over time, particularly for drugs that may be used chronically.

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.

2.7.4.1 Exposure to the Drug

2.7.4.1.1 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 the section 2.7.4.7 Appendix). 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 Section 2.7.3.2 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.

2.7.4.1.2 Overall Extent of Exposure

A table (see example provided in the section 2.7.4.7 Appendix) 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/m^2 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.

2.7.4.1.3 Demographic and Other Characteristics of Study Population

A summary table should provide the reader with an overview of the demographic characteristics (Table 2.7.4.2) 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.

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate subsections of Section 2.7.4.2.1 and the tables that are not embedded in the text should be placed in the section 2.7.4.7 Appendix.

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 of estimates 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 real differences. 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 drug-related, 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 a particular concomitant therapy.
- studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are 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 be influenced by inspection of individual study results. Whatever methods are used, it should be recognised that, as for results of single studies, any numerical rate is often only a rough approximation of reality.

When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is common to combine the numerator events and the denominators for the selected studies. Other methods for pooling results across studies are available, e.g., weighting data from studies on the basis of study size or inversely to their variance.

If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose administration, or in methods of collecting adverse event data).

Adverse events should be described as shown in the individual study report (ICH E3). In combining data from many studies, it is important to use standardised terms to describe events and collect synonymous terms under a single preferred term. This can be done with a standard dictionary, and the MedDRA terminology (ICH M1 guideline) should be used. Until MedDRA can be fully implemented, other dictionaries can be used, but should be specified. Frequencies should be presented for preferred terms and for appropriately defined groupings. Examination of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help in assessing the clinical importance of adverse events. These rates can be added to the adverse event rate tables, or can be presented in separate tables. Overall discontinuation rates by study may be useful but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.

2.7.4.2.1.1 Common Adverse Events

Tabular displays of adverse event rates (see the section 2.7.4.7 Appendix) should be used to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. It should be noted that while causality categories may be reported, if used, the presentation of the data should include total adverse events (whether deemed related or unrelated to treatment); evaluations of causality are inherently subjective and may exclude unexpected adverse events that are in fact treatment related. Additionally,

comparisons of rates of adverse events between treatment and control groups in individual trials should be summarised here. It is often useful to tabulate rates in selected trials (see example table 2.7.4.4, in the Section 2.7.4.7 Appendix).
It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to relevant factors, including:

- dosage;
- mg/kg or mg/m^2 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 examination of time of onset and duration for these drug-related events.

Rigorous statistical evaluations of the possible relationship of specific adverse events to each of the above factors are often unnecessary. It may be apparent from initial display and inspection of the data that there is no evidence of a significant relationship to demographic or other baseline features. In that case, no further analysis of these particular factors is needed. Further, it is not necessary that all such analyses be presented in this report. When the safety analyses are too extensive to be presented in detail in this report, they may be presented in a separate report in Module 5, section 5.3.5.3, and summarised here.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates.

2.7.4.2.1.2 Deaths

A table in the Section 2.7.4.7 Appendix 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 Section 2.7.4.2.1.1 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 prolongation-associated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.

2.7.4.2.1.3 Other Serious Adverse Events

Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the drug use was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events using the ICH E2A definitions. Results of analyses or assessments of serious adverse events across studies should be presented. Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Potential relationships to the factors listed in Section 2.7.4.2.1.1 should also be considered.

2.7.4.2.1.4 Other Significant Adverse Events

Marked haematologic and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed.

Events that led to premature discontinuation of study drug represent an important safety concern and deserve particular attention 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 reflects the severity and perceived importance of the event to patient and physician. Second, discontinuation may represent a drug-related event not yet recognised as drug related. Adverse events leading to treatment discontinuation should be considered possibly drug-related even if this was not recognised initially and even if the event was thought to represent intercurrent illness. Reasons for premature treatment discontinuations should be discussed and rates of discontinuations should be compared across studies and compared with those for placebo and/or active control treatment. In addition, the study data should be examined for any potential relationships to the factors listed in Section 2.7.4.2.1.1.

2.7.4.2.1.5 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 the context 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 should be placed in subsections of section 2.7.4.2.1.5, labelled as 2.7.4.2.1.5.**1**, 2.7.4.2.1.5.**2**, etc., and titled by the organ system under consideration. The list of organ systems to be addressed and the approach to grouping certain events should be selected as appropriate to best present the adverse event data for the medicinal product. If some adverse events tend to occur in syndromes (e.g., influenza-like syndrome, cytokine release syndrome), the sponsor may choose to create some subsections of 2.7.4.2.1.5 for syndromes rather than organ systems.

The same data and summarisations should generally not be repeated in more than one subsection of Section 2.7.4.2.1. Instead, a summary presentation may be placed in one subsection and cross-referenced as needed in the other.

2.7.4.2.2 Narratives

The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance (as described in ICH E3 individual study reports) should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, if there is such a report. In cases where there is no individual study report (e.g., if many open studies are pooled as part of a safety analysis and are not individually described), narratives can be placed in Module 5, Section 5.3.5.3. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug.

2.7.4.3 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 section 2.7.4.2.1.3 or 2.7.4.2.1.4. 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 in standard 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 centres 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 Section 2.7.4.2.1.1 should also be considered.

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

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

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

This section should summarise safety data pertinent to individualising therapy or patient management on the basis of demographic and other factors defined as "intrinsic ethnic factors" in ICH E5. These factors include age, sex, height, weight, lean body mass, genetic polymorphism, body composition, other illness and organ dysfunction. Safety in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Analysis of the impact of such factors 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. If a sufficiently large number of subjects with a given co-morbid condition such as hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to assess whether the co-morbid 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.

2.7.4.5.2 Extrinsic Factors

This section should summarise safety data pertinent to individualising therapy or patient management on the basis of factors defined as "extrinsic ethnic factors" in ICH E5. These are factors associated with the patient environment. Examples are the medical environment, use of other drugs (see 2.7.4.5.3, 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.

2.7.4.5.3 Drug Interactions

Studies on potential drug-drug or drug-food interactions should be summarised in the Summary of Clinical Pharmacology Studies section of the CTD (Section 2.7.2). 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.

2.7.4.5.4 Use in Pregnancy and Lactation

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

2.7.4.5.5 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.

2.7.4.5.6 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 cross-referenced to the nonclinical summary. Particularly susceptible patient populations should be identified.

2.7.4.5.7 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 section 2.7.3.5 in the Summary of Clinical Efficacy.

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

Safety data related to any impairment in the senses, co-ordination, 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.

2.7.4.6 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 Module 5. 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.

2.7.4.7 Appendix

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 sections 2.7.4.2.1, 2.7.4.2.2.3, and 2.7.4.3 of this guidance for additional discussion regarding the content of section 2.7.4 tables.

Table 2.7.4.1	Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure
Table 2.7.4.2	Demographic Profile of Patients in Controlled Trials
Table 2.7.4.3	Incidence of Adverse Events in Pooled Placebo and Active Controlled Trials
Table 2.7.4.4	Incidence of Adverse Events in the Largest Trials
Table 2.7.4.5	Patient Withdrawals by Study: Controlled Trials
Table 2.7.4.6	Listing of Deaths

2.7.5 Literature References

A list of references cited in the Clinical Summary should be provided. Copies of all important references should be provided in Module 5, Section 5.4. The reference list should indicate which references are available in Module 5, Section 5.4. All references that have not been provided should be available upon request.

2.7.6 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 Module 5, followed by all individual study synopses organised in the same sequence as the study reports in Module 5.

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 in Module 5. 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 2.7.1.1 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/L x hr)	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 2.7.1.2 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 2.7.2.1 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 2.7.3.1 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, Smith & Jones CRO	May-98 Ongoing as of May 2001 126/ 400	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 2.7.3.2 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 2.7.4.1 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 2.7.4.2 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	N (%)	N (%)	N (%)
18 - 40	N (%)	N (%)	N (%)
40 - 64	N (%)	N (%)	N (%)
65 - 75	N (%)	N (%)	N (%)
>75	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 2.7.4.3 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 2.7.4.4 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 2.7.4.5 Patient Withdrawals[3] 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.

[4] 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 followup).

[3] 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 2.7.4.6 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.

Module 3

Quality

Chemical-pharmaceutical and biological information for chemical active substances and biological medicinal products.

NTA, Volume 2B, CTD-Module 3

Edition July 2004

Concerning chemical pharmaceutical and biological documentation for chemical active substance(s) and biological medicinal products

The principle of GMP and the detailed guidelines are applicable to all operations which require the authorization referred to in Article 40 of Directive 2001/83/EC as modified. They are also relevant for all other large scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, for the preparation of products for use in clinical trials, and for wholesaling, were applicable.

All analytical test procedures described in the various sections of the chemical, pharmaceutical and biological documentation must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.

Scope of the Guideline

This document is intended to provide guidance on the format of the chemical pharmaceutical and biological documentation of a registration application for chemical active substance(s), biological medicinal products, for radiopharmaceuticals and their corresponding medicinal products.. This format may also be appropriate for certain other categories of products (Herbals, vaccines, blood,…). To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.

The text following the section titles is intended to be explanatory and illustrative only. The content of these sections should include relevant information described in existing CPMP-ICH or CPMP guidelines,

The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guideline.

In the "Body of Data" reference is made to existing CPMP-ICH or CPMP guidelines which should be taken into account when compiling the chemical, pharmaceutical and biological part of the application. Further additional guidelines, which may be appropriate are listed in the Annex to Module 3. The following CPMP guidelines have a more general character and also, need to be considered, where relevant:

"Limitations to the use of Ethylene Oxide in the Manufacture of Medicinal Products"
"The use of Ionising radiation in the manufacture of medicinal products"
"Dry Powder Inhalers"
"On Quality Of Modified Release Products: A: Oral Dosage Forms B: Transdermal Dosage Forms Section I (Quality)"
"Investigation of Chiral Active Substances"
"*Radiopharmaceuticals*"
"Production and Quality Control of Medicinal Products derived by Recombinant DNA Technology"
"Production and Quality Control of Cytokine Products derived by Biotechnological Processes"
"Production and Quality Control of Monoclonal Antibodies"
"Gene Therapy Product Quality Aspects in the Production of Vectors and Genetically Modified Somatic Cells"
"Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use"
"Note for Guidance on medicinal gases - pharmaceutical documentation"
"Note for Guidance on requirements for pharmaceutical documentation for pressurised metered dose inhalation products"
"Note for Guidance on quality of water for pharmaceutical use"
"use of Near Infrared Spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations"
"Note for Guidance on Allergen products"
"Note for Guidance on Harmonisation of Requirements for Influenza Vaccines"
"Points to consider on the development of live attenuated influenza vaccines"
"Note for Guidance on production and quality control of animal immunoglobulins and immunosera for human use"
"Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines"
"Note for Guidance on Plasma-derived Medicinal Products"

References to guidelines are inserted to assist applicants. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines, as revised or maintained, are taken into account in the preparation of each part of their dossier. The guidelines referenced in each section provide useful information on the content expected in that section. However this list should not be regarded as comprehensive.
Wherever relevant, the requirements of the European Pharmacopoeia apply: specific monographs, general monographs and general chapters.

3.1 Table of Contents of Module 3

A Table of Contents for Module 3 should be provided.

3.2 Body of Data

3.2.S DRUG SUBSTANCE[1] (NAME, MANUFACTURER)

Reference CPMP Guidelines:
"On summary of requirements for active substances in part II of the dossier",including the Certification of Suitability of monographs of the European Pharmacopoeia.(see also NTA, Vol. 2B – introduction).
"Active Substance Master File procedure"

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example:

- Recommended International Nonproprietary Name (INN);
- Compendial name (e.g. European Pharmacopoeia) if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
- Chemical Abstracts Service (CAS) registry number.

Reference CPMP-Guidelines: "Chemistry of New Active Substance" and *"Chemistry of the Active Substance"*

3.2.S.1.2 Structure (name, manufacturer)

NCE:

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.
Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

Biotech:

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.
Reference CPMP Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

3.2.S.1.3 General Properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of Active Substance"*

[1] **For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance**

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances" and "Specifications – Test Procedures and Acceptance criteria for Biotechnological, Biological products"

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

NCE:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

Biotech:

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3, major equipment (details provided in 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in 3.2.S.2.4.).

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.).

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4.).

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used

for storage of the drug substance (details in 3.2.S.6.) and storage and shipping conditions for the drug substance should be described.

Reference CPMP-ICH Guidelines: "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin", "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products".

3.2.S.2.3 Control of Materials (name, manufacturer)

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation. (Details in 3.2.A.2 for both NCE and Biotech)

Reference CPMP Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*
Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products", "Use of bovine serum in the manufacture of human biological medicinal products".

Biotech:

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information for biologically-sourced materials should be provided. (Details in 3.2.A.2.)

Source, history, and generation of the cell substrate

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in CPMP-ICH Guidelines Q5B and Q5D.

Cell banking system, characterisation, and testing

Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in CPMP-ICH Guidelines Q5B and Q5D.

Reference CPMP-ICH Guidelines: "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin", " Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA

Derived Protein Products", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products", "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products"

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

Additionally for Biotech: Stability data supporting storage conditions should be provided.
Reference CPMP-ICH Guideline: "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products"

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

Biotech:

Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

NCE:

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in

producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference CPMP-ICH Guideline: "Impurities testing guideline: impurities in new drug substances

Biotech:

The developmental history of the manufacturing process, as described in 3.2.S.2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see Q6B for additional guidance). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference CPMP-ICH Guidelines: "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products", "Comparability of medicinal products containing biotechnology-derived proteins as active drug substance"

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

NCE:

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Reference CPMP-ICH Guideline: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances

Reference CPMP-Guidelines: "Chemistry of the New Active Substance" and *"Chemistry of the Active Substance"*

Biotech:

For desired product and product-related substances, details should be provided on primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.

Reference CPMP-ICH Guideline: "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided.

Reference CPMP-ICH Guidelines: "Impurities testing guideline: impurities in new drug substances", "Impurities: residual solvents", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP-Guidelines: "Control of Impurities of Pharmacopoeial Substances"

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification for the drug substance should be provided.

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP-Guidelines: "Chemistry of the New Active Substance", "Chemistry of the Active Substance"and "Control of Impurities of Pharmacopoeial Substances"

3.2.S.4.2 Analytical Procedures (name, manufacturer)

The analytical procedures used for testing the drug substance should be provided.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP-Guidelines: "Control of Impurities of Pharmacopoeial Substances"

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
"Tests on Samples of Biological Origin"

3.2.S.4.4 Batch Analyses (name, manufacturer)

Description of batches and results of batch analyses should be provided.

Reference CPMP-ICH Guidelines: "Impurities testing guideline: impurities in new drug substances", "Impurities: residual solvents", "Specifications – Test Procedures and Acceptance Criteria for New drug substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specification should be provided.

Reference CPMP-ICH Guidelines: "Impurities testing guideline: impurities in new drug substances", "Impurities: residual solvents", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP-Guidelines: "Control of Impurities of Pharmacopoeial Substances"

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.S.6 Container Closure System (name, manufacturer)

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the

drug substance, including sorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference CPMP-ICH Guidelines: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", ", "Evaluation of stability data", "On stability testing for a type II variation to a marketing authorisation", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products,"
Reference CPMP-Guidelines: "Chemistry of the New Active Substance" "Chemistry of the Active Substance", "On the declaration of storage conditions for medicinal products in the products particulars and for active substances", "on stability testing of existing active substances and related finished products"

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided.

Reference CPMP-ICH Guidelines: "Stability testing guidelines: stability testing of new drug substances and products", , "On stability testing for a type II variation to a marketing authorisation", "Evaluation of stability data", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products
Reference CPMP-Guideline: "on stability testing of existing active substances and related finished products"

3.2.S.7.3 Stability Data (name, manufacturer)

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference CPMP-ICH Guidelines: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "On stability testing for a type II variation to a marketing authorisation", "Evaluation of stability data", "Quality of Biotechnological Products: Stability Testing of Biotechnological / Biological Products"
Reference CPMP-Guideline: "on stability testing of existing active substances and related finished products"

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

A description of the drug product and its composition should be provided. The information provided should include, for example:

- **Description**[2] of the dosage form;
- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications):
- Description of accompanying reconstitution diluent(s); and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.2 Pharmaceutical Development (name, dosage form)

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Reference CPMP-ICH Guidelines: "On development pharmaceutics", "Annex to Development Pharmaceutics – Decision Trees for Selection of Sterilisation methods"
"Development Pharmaceutics for Biotechnological and Biological Products - Annex to NfG on Development Pharmaceutics"
Reference CPMP Guideline: "on investigation of bioavailability and bioequivalence"

3.2.P.2.1 Components of the Drug Product (name, dosage form)

3.2.P.2.1.1 Drug Substance (name, dosage form)

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content,

[2] For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P", as appropriate

solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients (name, dosage form)

The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

Reference CPMP Guideline: "Excipients in the Dossier for application for marketing authorisation of a medicinal product"

3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.2.1 Formulation Development (name, dosage form)

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

Reference CPMP-ICH Guideline: "Comparability of medicinal products containing biotechnology-derived proteins as active drug substance"

3.2.P.2.4 Container Closure System (name, dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

3.2.P.2.5 Microbiological Attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Reference CPMP Guideline: "Guideline on the use of antioxidants and preservatives in medicinal products"

3.2.P.2.6 Compatibility (name, dosage form)

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Reference CPMP Guideline: "On Manufacture of the finished dosage form"

3.2.P.3.2 Batch Formula (name, dosage form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

Reference CPMP Guideline: " On Manufacture of the finished dosage form"

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

Additionally for Biotech see 3.2.A.1 for facilities, if appropriate.

Reference CPMP Guideline: " On Manufacture of the finished dosage form"

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "Specifications - Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products - Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP Guideline: " On Manufacture of the finished dosage form"

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

Reference CPMP-ICH Guideline: "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP Guidelines: " On Manufacture of the finished dosage form", "Process Validation", "Parametric Release"

3.2.P.4 Control of Excipients (name, dosage form)

Reference CPMP Guidelines: "Excipients in the Dossier for application for marketing authorisation of a medicinal product", "Guideline on the use of antioxidants and preservatives in medicinal products"

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided.

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.4.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.4.4 Justification of Specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

Reference CPMP-ICH Guidelines: "Impurities: residual solvents", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.A.2).

Reference CPMP-ICH Guidelines: "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin", "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products",

"Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP/CVMP Guideline: "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products"

3.2.P.4.6 Novel Excipients (name, dosage form)

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).

Reference CPMP Guideline: "On development pharmaceutics"

3.2.P.5 Control of Drug Product (name, dosage form)

Reference CPMP Guideline: "Specifications and Control Tests on the finished product"

3.2.P.5.1 Specification(s) (name, dosage form)

The specification(s) for the drug product should be provided.

Reference CPMP-ICH Guidelines: "Impurities in new drug products", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.5.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the drug product should be provided.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

Reference CPMP-ICH Guidelines: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.5.4 Batch Analyses (name, dosage form)

A description of batches and results of batch analyses should be provided.

Reference CPMP-ICH Guidelines: "Impurities in new drug products", " Impurities: residual solvents", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances

and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

Reference CPMP-ICH Guidelines: "Impurities in new drug products", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.5.6 Justification of Specification(s) (name, dosage form)

Justification for the proposed drug product specification(s) should be provided.

Reference CPMP-ICH Guidelines: "Impurities in new drug products", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.6 Reference Standards or Materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".

Reference CPMP-ICH Guidelines: "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"

3.2.P.7 Container Closure System (name, dosage form)

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

Reference CPMP Guideline: "Plastic Primary Packaging Materials".

3.2.P.8 Stability (name, dosage form)

Reference CPMP Guideline: "On reduced stability testing - bracketing and matrixing"

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

Reference CPMP-ICH Guidelines: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", "Impurities in new drug products", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products", "Specifications - Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products - Chemical Substances"
Reference CPMP Guidelines: "on stability testing of existing active substances and related finished products ", "On maximum shelf-life for sterile products for human use after first opening or following reconstitution", "On the declaration of storage conditions for medicinal products in the products particulars and for active substances", "In-Use stability testing of human medicinal products"

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

The post-approval stability protocol and stability commitment should be provided.

Reference CPMP-ICH Guidelines: "Stability testing guidelines: stability testing of new drug substances and products", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products",
Reference CPMP Guideline: " on stability testing of existing active substances and related finished products "

3.2.P.8.3 Stability Data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterisation of impurities is located in 3.2.P.5.5.

Reference CPMP-ICH Guidelines: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products"
Reference CPMP Guidelines: " on stability testing of existing active substances and related finished products ", "In-Use stability testing of human medicinal products"

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

Biotech:

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

Reference CPMP-ICH Guidelines: "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP Guideline: "Minimizing the Risk of Transmitting animal Spongiform Encephalopathy Agents via Medicinal Products"

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable.
Reference CPMP-ICH Guidelines: "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin", "Derivation and Characterisation of

Cell Substrates Used for Production of Biotechnological/ Biological Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP Guideline: " virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses"

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3).

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.S.2.4 and 3.2.P.3.4).

Viral Testing of Unprocessed Bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5).

Reference CPMP-ICH Guidelines: "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin", "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products", "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products"
Reference CPMP Guideline: "Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses"

3.2.A.3 Excipients

Module 3.2.R
Regional Information

For EU

Any additional drug substance/active substance and/or drug product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance.

- **Process Validation Scheme for the Drug Product**

  Reference CPMP-ICH Guideline: *Note for Guidance on Process Validation (CPMP/QWP/848/96, EMEA/CVMP/598/99)*

- **Medical Device**

- **Certificate(s) of Suitability**

- **Medicinal products containing or using in the manufacturing process materials of animal and/or human origin**

  Compliance with the Annex I to Dir. 2001/83/EC, Part I, Module 2, paragraph 3.2 (9)

  *"**(9)** Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance."*

In the case that scientific data to substantiate this compliance is included in the Quality Part of the dossier, then this data should be reviewed in the Quality Overall Summary (Module 2.3).

For all applications, the table A on '*Materials of animal origin covered by the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products'* should be completed .

TSE Certificates of Suitability (if available) are to be attached.

For materials of animal origin other than those covered by the *Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*, applicants are requested to complete the table B on '*Other materials of animal origin*'.

If an application relates to a medicinal product, which contains or uses in the manufacture materials of human origin, applicants are request to complete the table C on albumin and other human tissue derived products.

Table A : Materials of animal origin covered by the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products[i]

Medicinal product: (Invented name/INN)
Applicant:
Date of completion of table:

Name of material				
Name and address of manufacturer[ii]				
Species and tissue from which material is a derivative				
Country of origin of the source animals for the material cited				
Do you have a TSE-Certificate of Suitability[iii] **for the material of animal origin? If yes, please put number and date of certificate and attach a copy.**				
Use of material	**As active substances**			
	As excipient			
	As reagent/ culture medium component used in routine manufacture			
	As reagent/ culture medium component used in establishment of new master cell banks[iv]			
	As reagent/ culture medium component used in establishment of working cell banks			
	Starting material used in manufacture of active substances			
	Starting material used in manufacture of excipient			
	Other, give details			

[i] Note For Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products, Jan 2004 (EMEA/410/01 rev2) or any future revision.

[ii] The manufacturer and not the supplier/broker of the material of animal origin should be mentioned. For the same material from different manufacturers, use a separate column for each manufacturer.

[iii] From 1 January 2000, manufacturers of materials of animal origin can submit a dossier to the European Pharmacopoeia to obtain a Certificate of Suitability in accordance with the monograph : 'Products at risk of transmitting animal spongiform encephalopathies'.

[iv] Materials of ruminant origin used in the establishment of **existing** master cell banks should be included in Table B.

Table B : Other materials of animal origin[i]

Medicinal product: (Invented name/INN)
Applicant:
Date of completion of table:

Name of material				
Name and address of manufacturer				
Species and tissue from which material is a derivative				
Country of origin of the source animals for the material cited				
Use of material	**As active substances**			
	As reagent/ culture medium component used in routine manufacture			
	As reagent/ culture medium component used in establishment of master cell banks[ii]			
	As reagent/ culture medium component used in establishment of working cell banks			
	Starting material used in manufacture of active substances			
	As excipient			
	Starting material used in manufacture of excipient			
	Other, give details			

[i] Materials not covered by the Note For Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products, Jan 2004 (EMEA/410/01 rev2) or any future revision

ii Materials of ruminant origin used in the establishment of existing master cell banks should also be included in this Table.

Table C : Albumin and other human tissue derived materials.

Medicinal product: (Invented name/INN)
Applicant:
Date of completion of table:

Name of Material				
Supplier				
Tissue from which material is a derivative				
Country (-ies) where donation took place				
Does the material have a Marketing Authorisation? **If yes, specify Member State(s) and MA number(s)**				
Use of Material:	**As active substances**			
	As excipient			
	As reagent / culture medium component			
	Other, please specify			

Module 3.3
Literature References

Key literature referenced should be provided, if applicable.

Annex to Module 3 (Updated June 2004)

A- List of references to quality guidelines

References to EU guidelines are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier.

The guidelines referenced below are available on the EMEA WebSite http://www.emea.eu.int or in Volume 3A of the "Rules Governing medicinal products in the EU"– Eudralex, available on the WebSite of the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm.

Although this annex will be updated regularly, applicants are advised to consult the EMEA Website for the latest versions or additions to the guidelines listed below.

General Guidelines

Document Title	Number/*version*
Validation of analytical methods: definitions and terminology (Q2A)	CPMP/ICH/381/95
Validation of analytical procedures methodology (Q2B)	CPMP/ICH/281/95
Note for guidance on development pharmaceutics	CPMP/QWP/155/96
Dry Powder Inhalers	CPMP/QWP/158/96
Annex to development pharmaceutics – Decision trees for selection of sterilisation methods	CPMP/QWP/054/98
Investigation of chiral active substances	3CC29a *Revision 1993*
Note for Guidance on radiopharmaceuticals	3AQ20a *Revision 1990*
Note for Guidance on the investigation of bio-availability and bioequivalence	CPMP/EWP/QWP/1401/98
Note for Guidance on Declaration of Storage Conditions A: In the product information of Medicinal Products and B: for Active Substances	CPMP/QWP/609/96 rev. 1
Revision of the Guideline on Excipients in the Package Leaflet	CPMP/463/00*

Active Substance Guidelines

Document Title	**Number/*version***
Chemistry of the active substances (Oct 91)	3AQ5a *Revision 1987*
Note for Guidance on the Chemistry of new active substances	CPMP/QWP/130/96 rev 1*
Appendix to the Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia – methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia	CPMP/EWP/49/01
Guideline on Control of impurities of pharmacopoeial substances: Compliance with the European Pharmacopoeia general monograph "Substances for pharmaceutical use" and general chapter "Control of Impurities in substances for pharmaceutical use"	CPMP/QWP/1529/04*
Stability testing: photostability testing of new drug substances and products (Q1B)	CPMP/ICH/279/95
Note for Guidance on impurities testing: Impurities in new drug substances (revision of CPMP/ICH/142/95) (Q3A)	CPMP/ICH/2737/99
Impurities: residual solvents (Q3C)	CPMP/ICH/283/95
Maintenance of document for Guidance on Impurities: residual solvents (Q3C)	CPMP/ICH/1507/02
Maintenance of Note for Guidance on Impurities: Residual solvents. PDE for tetrahydrofuran (THF) and N-methylpyrrolidone (NMP) (Q3C (M))	CPMP/ICH/1940/00
Note for Guidance and specifications – Test Procedure and acceptance criteria for new drug substances and new drug products – Chemical substances (Q6A)	CPMP/ICH/367/96
Note for Guidance on stability testing of new drug substances and products (Q1A)	CPMP/ICH/2736/99
Note for Guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (Q1D) – replaces CPMP/QWP/157/96	CPMP/ICH/4104/00
Guideline on stability testing: Stability testing of existing active substances and related finished products	CPMP/QWP/122/02 rev 1*
Note for Guidance on summary of requirements for active substances in part II of the dossier	CPMP/QWP/297/97
Guideline on Active Substance Master File Procedure	CPMP/QWP/227/02*

Medicinal Product Guidelines

Document Title	**Number/*version***
Specifications and control tests on the finished duct	3AQ11a *Revision 1991*
Limitations to the use of ethylene oxide in the manufacture of medicinal products	CPMP/QWP/2845/00
The use of ionising radiation in the manufacture of medicinal products	3AQ4a *Revision 1991*
Plastic primary packaging materials	3AQ10a *Revision February 1994*
Guideline on the use of antioxidants and preservatives in medicinal products	CPMP/QWP/115/95
Excipients in the dossier for application for marketing authorisation of a medicinal product	3AQ91 *Revision February 1994*
Stability testing: photostability testing of new drug substances and products (Q1B)	CPMP/ICH/279/95
Stability testing requirements for new dosage forms (Q1C)	CPMP/ICH/280/95
Impurities in new drug products (Q3B (R))	CPMP/ICH/2738/99
Impurities: residual solvents (Q3C)	CPMP/ICH/283/95
Maintenance of document for Guidance on Impurities: residual solvents (Q3C)	CPMP/ICH/1507/02
Note for Guidance and specifications – Test procedure and acceptance criteria for new drug substances and new drug products – Chemical substances (Q6A)	CPMP/ICH/367/96
Revision of Note for Guidance on stability testing: Stability testing of new active substance and medicinal products (Q1A(R))	CPMP/ICH/2736/99
Note for Guidance on manufacture of the finished dosage form	CPMP/QWP/486/95
Note for Guidance on maximum shelf-life sterile products for human use after first opening or following reconstitution	CPMP/QWP/159/96
Guidance on stability of established active ingredients and finished products	CPMP/QWP/556/96
Note for Guidance on stability testing for a type II variation to a marketing authorisation	CPMP/QWP/576/96
Note for Guidance on the declaration of storage conditions for medicinal products in the products particulars	CPMP/QWP/609/96
Note for Guidance on quality of modified release products: A. Oral dosage forms, B. Transdermal dosage forms Section I (Quality)	CPMP/QWP/604/96
Note for Guidance on process validation	CPMP/QWP/848/96 EMEA/CVMP/598/99
Note for Guidance on in-use stability testing of human medicinal products	CPMP/QWP/2934/99
Note for Guidance on start of shelf-life of the finished dosage form	CPMP/QWP/072/96
Note for Guidance on parametric release	CPMP/QWP/3015/99

Note for guidance on Quality of water for pharmaceutical use	CPMP/QWP/158/01
Guideline on Medicinal Gases – Pharmaceutical Documentation	CPMP/QWP/1719/00
Note for Guidance on Requirements for pharmaceutical documentation for pressurised metered dose inhalation products	CPMP/QWP/2845/00
Note for Guidance on the use of Near Infrared Spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations	CPMP/QWP/3309/01
Evaluation of stability data (Q1E)	CPMP/ICH/420/02
Stability data package for registration: climatic Zones III and IV (Q1F)	CPMP/ICH/421/02
Note for Guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (Q1D) – replaces CPMP/QWP/157/96	CPMP/ICH/4104/00
Guideline on stability testing: Stability testing of existing active substances and related finished products	CPMP/QWP/122/02 rev 1*

B- List of references to biotechnology guidelines

References to EU guidelines are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier.

The guidelines referenced below are available on the EMEA WebSite http://www.emea.eu.int or in Volume 3A of the "Rules Governing medicinal products in the EU"– Eudralex, available on the WebSite of the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm.

Although this annex will be updated regularly, applicants are advised to consult the EMEA Website for the latest versions or additions to the guidelines listed below.

General Guidelines

Document title	**Number/*version***
Production and quality control of medicinal products derived by recombinant DNA technology	3AB1a, *Revision December 1994*
Production and quality control of cytokine products derived by biotechnological processes	3AB3a, *Revision February 1990*
Production and quality control of monoclonal antibodies	3AB4a, *Revision December 1994*
Use of transgenic animals in the manufacture of biological medicinal products for human use	3AB7a, *Revision December 1994*
Tests on samples of biological origin	3AB11a
Gene therapy product quality aspects in the production of vectors and genetically modified somatic cells	3AB6a, *Revision December 1994*
Guideline on Comparability of Medicinal Products containing Biotechnology-Derived Proteins as Active Substances: Quality issues	CPMP/BWP/3207/00/Rev1*
Lactose prepared using calf rennet: risk assessment in relationship to bovine spongiform encephalopathies (BSE).	EMEA/CPMP/571/02
Final EU recommendations for the influenza vaccine composition for the season 2003/2004	CPMP/BWP/6011/03
Revised CPMP position statement on CJD and Plasma-derived and Urine-derived medicinal products	CPMP/BWP/2879/02
Position Statement on West Nile Virus and Plasma-Derived Medicinal Products	CPMP/BWP/3752/03*

Guidance on the Description of composition of pegylated (conjugated) proteins in the SPC	CPMP/BWP/3068/03*
Note for Guidance on the Warning on transmissible agents in SPCs and Package Leaflets for Plasma-Derived Medicinal Products.	CPMP/BPWG/BWP/561/03*
EMEA workshop on viral safety of plasma-derived medicinal products with particular focus on non-enveloped viruses; incl. Addendum representing the conclusions and recommendations of the BWP & BPWG	CPMP/BWP/BPWG/4080/00 CPMP/BWP/BPWG/93/01

Active Substance and Medicinal Products Guidelines

Document title	**Number/v*ersion***
Note for Guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses	CPMP/BWP/268/95
Note for Guidance on allergen products	CPMP/BWP/243/96
Note for Guidance on harmonisation of requirements for influenza vaccines	CPMP/BWP/214/96
Cell Culture inactivated influenza vaccines – Annex to Note for Guidance on harmonisation of requirements for influenza vaccines	CPMP/BWP/2490/00
Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application	CPMP/VEG/4717/03*
Points to consider on the development of live attenuated influenza vaccines	CPMP/BWP/2289/01
Note for Guidance on pharmaceutical and biological aspects of combined vaccines	CPMP/BWP/477/97
Development pharmaceutics for biotechnological and biological products - Annex to Note for Guidance on development pharmaceutics (CPMP/QWP/155/96)	CPMP/BWP/328/99
TSE Revision of Joint CPMP/CVMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.	EMEA/410/01 rev 2*
Note for Guidance on plasma-derived medicinal products	CPMP/BWP/269/95, *Revision 3*
Note for Guidance on Production and quality control of animal immunoglobulins and immunosera for human use	CPMP/BWP/2712/02

Note for Guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products (Q6B)	CPMP/ICH/365/96
Note for Guidance on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (Q5A)	CPMP/ICH/295/95
Note for Guidance on quality of biotechnological products: analysis of the expression construct in cell lines used for production of r-DNA derived protein products (Q5B)	CPMP/ICH/139/95
Note for Guidance on quality of biotechnological products: stability testing of biotechnological/biological products (Q5C)	CPMP/ICH/138/95
Note for Guidance on quality of biotechnological products: derivation and characterisation of Cell substrates used for production of biotechnological/ biological products (Q5D)	CPMP/ICH/294/95
Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products	CPMP/BWP/3088/99
Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy	CPMP/BWP/41450/98
Points to Consider on the Reduction, Elimination or Substitution of Thiomersal in Vaccines	CPMP/BWP/2517/00
Note for Guidance on the Use of bovine serum in the manufacture of human biological medicinal products	CPMP/BWP/1793/02*
Note for Guidance on Pharmaceutical aspects of the product information for human vaccines	CPMP/BWP/2758/02*
Position Statement on the Quality of water used in the production of vaccines for parenteral use	CPMP/BWP/1571/02 rev. 1*
Guideline on the Scientific Data Requirements for a Plasma Master File (PMF)`	CPMP/BWP/3794/03*
Guideline on Requirements for Plasma Master File (PMF) Certification	CPMP/BWP/4663/03*
Vaccine Antigen Master File: Guideline on requirements for Vaccine Antigen Master File (VAMF) Certification	CPMP/BWP/4548/03*
Guideline on the scientific data requirements for a Vaccine Antigen Master File (VAMF)	CPMP/BWP/3734/03*

Development of Vaccinia Virus Based Vaccines against Smallpox	EMEA/CPMP/1100/02

* New Guideline.

Module 4

Nonclinical Study Reports

NTA, Volume 2B, CTD-Module 4

Final-Revision 2 - Edition July 2004

This guidance presents an agreed format for the organisation of the nonclinical reports in the Common Technical Document for applications that will be submitted to Regulatory Authorities. This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual-animal data is in the study report or as an appendix to the study report.

4.1 TABLE OF CONTENTS OF MODULE 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

4.2 STUDY REPORTS

The study reports should be presented in the following order:

4.2.1 Pharmacology
- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics
- 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology
- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
  - 4.2.3.3.1 In vitro
  - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
  - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
  - 4.2.3.5.1 Fertility and early embryonic development
  - 4.2.3.5.2 Embryo-fetal development
  - 4.2.3.5.3 Prenatal and postnatal development, including maternal function
  - 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies (if available)
  - 4.2.3.7.1 Antigenicity
  - 4.2.3.7.2 Immunotoxicity
  - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
  - 4.2.3.7.4 Dependence
  - 4.2.3.7.5 Metabolites
  - 4.2.3.7.6 Impurities
  - 4.2.3.7.7 Other

4.3 LITERATURE REFERENCES

Annex to Module 4 (Updated June 2004)

List of references to non-clinical guidelines

References to EU guidelines are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier.

The guidelines referenced below are available on the EMEA WebSite http://www.emea.eu.int or in Volume 3B of the "Rules Governing medicinal products in the EU"– Eudralex, available on the WebSite of the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm.

Although this annex will be updated regularly, applicants are advised to consult the EMEA Website for the latest versions or additions to the guidelines listed below.

Section 4.2.1 Pharmacology

Safety pharmacology studies for human pharmaceuticals	CPMP/ICH/539/00 (ICH S7A)
Points to Consider on the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products	CPMP/SWP/986/96

Section 4.2.2 Pharmacokinetics

Pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals	EudraLex vol. 3B
Toxicokinetics: the assessment of systemic exposure in toxicity studies	CPMP/ICH/384/95 (ICH S3A)
Pharmacokinetics: Guidance for repeated dose tissue distribution studies	CPMP/ICH/385/95 (ICH S3B)

Section 4.2.3 Toxicology

Note for Guidance on single dose toxicity	Eudralex vol. 3B
Note for Guidance on repeated dose toxicity	CPMP/SWP/1042/99

Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)	CPMP/ICH/300/95 (ICH S4A)
Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals	CPMP/ICH/141/95 (ICH S2A)
Genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals	CPMP/ICH/174/95 (ICH S2B)
Guideline on carcinogenic potential	Eudralex vol. 3B (to be updated and replaced by Update of Note for Guidance on Carcinogenic Potential CPMP/SWP/2877/00)
Note for Guidance on Carcinogenic potential	CPMP/SWP/2877/00
Guideline on the need for carcinogenicity studies of pharmaceuticals	CPMP/ICH/140/95 (ICH S1A)
Carcinogenicity: testing for carcinogenicity of pharmaceuticals	CPMP/ICH/299/95 (ICH S1B)
Dose selection for carcinogenicity studies of pharmaceuticals	CPMP/ICH/383/95 (ICH S1C)
Addendum to Note for Guidance on dose selection for carcinogenicity studies of pharmaceuticals: addition of a limit dose and related doses	CPMP/ICH/366/96 (ICH S1C[R])
Points to consider on the Non-clinical assessment of the carcinogenic potential of human insulin analogues	CPMP/SWP/372/01
SWP Conclusions and recommendations with regard to the use of genetically modified animal models for carcinogenicity assessment	CPMP/SWP/2592/02
Reproductive toxicology: detection of toxicity to reproduction for medicinal products including toxicity to male fertility	CPMP/ICH/386/95(ICH S5A) and CPMP/ICH/136/95(ICH S5B)
Points to consider on the Need for assessment of reproduction toxicity of human insulin analogues	CPMP/SWP/2600/01
Note for Guidance on non-clinical local tolerance testing of medicinal products	CPMP/SWP/2145/00

General Guidelines

Preclinical safety evaluation of biotechnology-derived pharmaceuticals	CPMP/ICH/302/95 (ICH S6)
Note for Guidance on preclinical pharmacological and toxicological testing of vaccines	CPMP/SWP/465/95
Note for Guidance on the pre-clinical evaluation of anti-cancer medicinal products	CPMP/SWP/997/96
Replacement of animal studies by in-vitro models	CPMP/SWP/728/95
Environmental risk assessment for human medicinal products containing or consisting of GMOs (under revision)	EudraLex vol.3B
Note for Guidance on Photosafety testing	CPMP/SWP/398/01
Position Paper on the non-clinical safety studies to support clinical trials with a single micro dose	CPMP/SWP/2599/02
Note for Guidance on comparability of medicinal products containing biotechnology-derived proteins as active substance - annex on non-clinical and clinical issues	CPMP/3097/02*
Revised Public Statement on Thiomersal in vaccines for Human Use	CPMP/VEG/1194/04 v02*
Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application	CPMP/VEG/4717/03*

* new guidelines

Module 5

Clinical Study Reports

NTA, Volume 2B, CTD-Module 5

Final-Revision 2-July 2004

Preamble

Through the ICH process, a guideline has been published on the structure and content of clinical study reports (E3). This document provides guidance on the organisation of these study reports, other clinical data, and references within a Common Technical Document (CTD) for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.

This guidance is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

Detailed Organization of Clinical Study Reports and Related Information in Module 5

This guidance 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.

5.1 TABLE OF CONTENTS

A table of contents for the study reports should be provided as follows:

5.2 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 5.1 of this guidance. 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 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.3 CLINICAL STUDY REPORTS

5.3.1 Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. 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 Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include:

- 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;
- dosage form proportionality studies; and
- food-effect studies.

5.3.1.2 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

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product;
- the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches; and
- similar drug products from different manufacturers.

5.3.1.3 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 Section 5.3.1.3. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD.

5.3.1.4 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 Section 5.3.1.4 and referenced in the appropriate individual study reports.

5.3.2 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 (Module 4).

5.3.2.1 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 Section 5.3.3.

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

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

5.3.2.3 Reports of Studies Using Other Human Biomaterials

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

5.3.3 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 Sections 5.3.3.1 and 5.3.3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faeces 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 Section 5.3.3.1 to 5.3.3.2, 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 Sections 5.3.3.1 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorised as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organised in Sections 5.3.3.3 and 5.3.3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-PK-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 5.3.3.5.

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

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

5.3.3.2 Patient PK and Initial Tolerability Study Reports

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

5.3.3.3 Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section.

5.3.3.4 Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors, should be placed in this section.

5.3.3.5 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.

5.3.4 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 Section 5.3.5.

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 Section 5.3.4.1, and the reports for those studies conducted in patients should be placed in Section 5.3.4.2.

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 Section 5.3.5, not in Section 5.3.4.

5.3.4.1 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

5.3.4.2 Patient PD and PK/PD Study Reports

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

5.3.5 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 Section 5.3.5, 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 Section 5.3.5 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 Section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5.3.5 and referenced as necessary in other Sections 5.3.5, e.g., Section 5.3.5A, Section 5.3.5B.

5.3.5.1 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 Section 5.3.5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Section 5.3.5.1. 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 Section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in Section 5.3.5.1.

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in Section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 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 Section 5.3.5.3. 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. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical

studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.3.5.4 Other 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 Section 5.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Section 5.3.5.1;
- Reports of ongoing studies.

5.3.6 Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in Section 5.3.6.

5.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

5.4 LITERATURE REFERENCES

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

Table 5.1. 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, 50 mg 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, 50 mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomized placebo-controlled	Tablet, 50 mg, 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 and Safety; Population PK analysis	Randomized active-controlled	Tablet, 50 mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full

Annex to Module 5

(Updated June 2004)

List of references to clinical guidelines

References to EU guidelines are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier.

The guidelines referenced below are available on the EMEA WebSite http://www.emea.eu.int or in Volume 3B and C of the "Rules Governing medicinal products in the EU"– Eudralex, available on the WebSite of the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm.

Although this annex will be updated regularly, applicants are advised to consult the EMEA Website for the latest versions or additions to the guidelines listed below.

Document title	**Number/*version***
General efficacy	
Note for Guidance on the structure and content of clinical study report	CPMP/ICH/137/95 (ICH E3)
Note for Guidance on good clinical practice	CPMP/ICH/135/95 (ICH E6)
Explanatory Note and Comments to CPMP/ICH/135/95	CPMP/768/97
Note for Guidance on general considerations for clinical trials	CPMP/ICH/291/95 (ICH E8)
Note for Guidance on statistical principles for clinical trials	CPMP/ICH/363/96 (ICH E9)
Note for Guidance on choice of control group for clinical trials	CPMP/ICH/364/96 (ICH E10)
Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents	CPMP/EWP/239/95
Note for Guidance on fixed combination medicinal products	CPMP/EWP/240/95

Points to consider on switching between superiority and non-inferiority	CPMP/EWP/482/99
Points to consider on application with 1. meta-analyses; 2 one pivotal study	CPMP/EWP/2330/99
Points to consider on Missing data	CPMP/EWP/1776/99
Note for Guidance on clinical investigation of medicinal products for long-term use	EudraLex Vol. 3C
Note for Guidance on clinical investigation of chiral active substances	EudraLex Vol. 3C
Note for Guidance on co-ordinating investigator signature of clinical study report	CPMP/EWP/2747/00
Points to Consider on multiplicity issues in clinical trials	CPMP/EWP/908/99
Revised Points to consider on adjustment for baseline covariates	CPMP/EWP/2863/99
Points to Consider on the Clinical Requirements of modified release products submitted as a line extension of an existing Marketing Authorisation	CPMP/EWP/1875/03*
Note for Guidance on comparability of medicinal products containing biotechnology-derived proteins as active substance - annex on non-clinical and clinical issues	CPMP/3097/02*

Clinical Safety

Note for Guidance on population exposure: the extent of population exposure to assess clinical safety	CPMP/ICH/375/95 (ICH E1A)
Note for Guidance on Good clinical safety data management: Definitions and standards for expedited reporting	CPMP/ICH/377/95 (ICH E2A)
Note for Guidance on clinical safety data management: data elements for transmission of individual case safety reports	CPMP/ICH/287/95 (ICH E2B[M])
Note for Guidance on clinical safety data management: periodic safety update reports for marketed drugs	CPMP/ICH/288/95
Addendum – Clinical safety data management:	CPMP/ICH/774/03

periodic safety update reports for marketed drugs (E2C)	
Note for Guidance on recommendations on electronic transmission of individual case safety reports message specification	CPMP/ICH/285/95 (ICH M2[M])
Note for Guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals	CPMP/ICH/286/95 (ICH M3 [M])
Note for Guidance on medicines intended for long-term treatment of non-life threatening conditions	EudraLex Vol. 3C
Note for Guidance on clinical investigation of medicinal products for long-term use	EudraLex Vol. 3C
ICH –Post-Approval Safety data management: Note for Guidance on definitions and standards for expedited reporting (E2D)	CPMP/ICH/3945/03*

Clinical pharmacology

Note for Guidance on pharmacokinetic studies in man.	EudraLex Vol. 3C
Note for Guidance on dose response information to support drug registration	CPMP/ICH/378/95 (ICH E4)
Note for Guidance on ethnic factors in the acceptability of foreign clinical data	CPMP/ICH/289/95 (ICH E5)
Note for Guidance on the investigation of drug interactions	CPMP/EWP/560/95
Note for Guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation)	CPMP/EWP/280/96
Note for Guidance on the investigation of bio-availability and bioequivalence	CPMP/EWP/QWP/1401/98

Special populations

Note for Guidance on studies in support of special populations: geriatrics	CPMP/ICH/379/95 (ICH E7)
Note for Guidance on Clinical Investigation of medicinal products in the paediatric population	CPMP/ICH/2711/99 (ICH E11)

Central Nervous System

Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia	CPMP/EWP/559/95
Appendix to the Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia – methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia	CPMP/EWP/49/01
Note for Guidance on clinical investigation of hypnotic medicinal products.	EudraLex vol. 3C
Note for Guidance on clinical investigation of medical products in the treatment of generalised anxiety disorder, panic disorder and obsessive-compulsive disorder.	EudraLex vol. 3C
Note for Guidance on medicinal products in the treatment of Alzheimer's disease	CPMP/EWP/553/95
Note for Guidance on clinical investigation of medicinal products in the treatment of Parkinson's disease	CPMP/EWP/563/95
Note for Guidance on Clinical investigation of medicinal products in the treatment of epileptic disorders	CPMP/EWP/566/98 *rev. 1*
Points to consider on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis	CPMP/EWP/565/98
Note for Guidance on clinical investigation of medicinal products for bipolar disorder	CPMP/EWP/567/98
Note for Guidance on clinical investigation of medicinal products for the treatment of multiple sclerosis	CPMP/EWP/561/98
Note for Guidance on Clinical investigation of medicinal products in the treatment of depression	CPMP/EWP/518/97 *rev. 1*
Revised Note for Guidance on clinical investigation of medicinal products for treatment of nociceptive pain	CPMP/EWP/612/00 *rev*. 1

Note for Guidance on Clinical Investigation of Medicinal Products for the treatment of migraine	CPMP/EWP/788/01*

Cardio-vascular system

Note for Guidance on clinical investigation of medicinal products in the treatment of hypertension	CPMP/EWP/238/95 *rev. 1*
Note for Guidance on antiarrhythmics	CPMP/EWP/237/95
Note for Guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease	CPMP/EWP/563/98
Note for Guidance on Clinical investigation of medicinal products in the treatment of cardiac failure	CPMP/EWP/235/95 *rev.1*
Note for Guidance on the clinical investigation of anti-anginal medicinal products in stable angina pectoris	CPMP/EWP/234/95
Note for Guidance on the clinical investigation of medicinal products in the treatment of chronic peripheral arterial occlusive disease	CPMP/EWP/714/98
Points to consider on clinical investigation of new medicinal products for the treatment of acute coronary syndrome (ACS) without persistent ST-segment elevation	CPMP/EWP/570/98
Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk	CPMP/EWP/707/98
Points to consider on clinical investigation of medicinal products for the treatment of acute stroke	CPMP/EWP/560/98
Note for Guidance on Clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease	CPMP/EWP/714/98 *rev. 1*
Points to Consider on the Clinical development of fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial infarction (STEMI)	CPMP/EWP/967/01*

Haematology/Cancer

Note for Guidance on Clinical trials with haematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy	CPMP/EWP/555/95
Points to consider on endpoints in clinical studies with haematopoietic growth factors for mobilisation of stem cells	CPMP/EWP/197/99
Note for Guidance on Evaluation of Anticancer medicinal products in man Note for Guidance on Evaluation of Anticancer medicinal products in man – Addendum on Paediatric oncology	CPMP/EWP/205/95 rev. 2* CPMP/EWP/569/02*

Blood products

Note for Guidance on the clinical investigation of human plasma derived Factor VIII and IX products	CPMP/BPWG/198/95 *Rev. 1*
Note for Guidance on the clinical investigation of recombinant Factor VIII and IX products	CPMP/BPWG/1561/99
Core SPC for human albumin	CPMP/PHVWP/BPWG/2231/99
Core SPC for human anti-D immunoglobulin for intravenous and/or intramuscular use	CPMP/BPWG/574/99
Note for Guidance on the clinical investigation of human normal Immunoglobulin for intravenous administration (IVIg)	CPMP/BPWG/388/95 *Rev 1*
Note for Guidance on the clinical investigation of human anti-D immunoglobulin for intravenous and/or intramuscular use	CPMP/BPWG/575/99
Note for Guidance on the clinical investigation of plasma derived antithrombin products	CPMP/BPWG/2220/99
Note for Guidance on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use	CPMP/BPWG/283/00
Core SPC for human normal immunoglobulin (IVIg) for intravenous administration	CPMP/BPWG/859/95 Rev. 1

Core SPC for human normal immunoglobulin for subcutaneous and intramuscular use	CPMP/BPWG/282/00
Core SPC for human plasma derived and recombinant coagulation Factor VIII products	CPMP/BPWG/1619/99
Core SPC for human plasma derived and recombinant coagulation Factor IX products	CPMP/BPWG/1625/99
Core SPC for Human Plasma derived antithrombin	CPMP/BPWG/3226/99
Core SPC for human tick-borne encephalitis immunoglobulin for intramuscular use	CPMP/BPWG/3732/02*
Core SPC for human tetanus immunoglobulin for intramuscular use	CPMP/BPWG/3730/02*
Core SPC for human rabies immunoglobulin for intramuscular use	CPMP/BPWG/3728/02*

Anti-infectives

Note for Guidance on clinical evaluation of new vaccines	CPMP/EWP/463/97
Note for Guidance on Evaluation of Medicinal Products indicated for treatment of bacterial infections.	CPMP/558/95 rev. 1*
Note for Guidance on pharmacodynamic section of the SPC for anti-bacterial medicinal products	CPMP/EWP/520/96
Points to consider in the assessment of anti-HIV medicinal products	CPMP/602/95 – *Rev. 3*
Note for Guidance on the clinical development of medicinal products for treatment of HIV infection	CPMP/EWP/633/02
Points to consider on wording of helicobacter pylori eradication therapy in selected SPC sections	CPMP/EWP/863/98
Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products	CPMP/EWP/2655/99
Note for Guidance on Development of vaccinia based vaccines against smallpox	CPMP/1100/02
Points to consider on the clinical evaluation of new agents for invasive fungal infections	CPMP/EWP/1343/01

Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application	CPMP/VEG/4717/03*

Endocrinology

Note for Guidance on postmenopausal osteoporosis in women	CPMP/EWP/552/95 *Rev. 1*
Note for Guidance on clinical investigation of drug used for weight control	CPMP/EWP/281/96
Note for Guidance on clinical investigation of steroid contraceptives in women	CPMP/EWP/519/98
Points to consider on hormone replacement therapy	CPMP/EWP/021/97
Note for Guidance on Clinical investigation of medicinal products in the treatment of diabetes mellitus	CPMP/EWP/1080/00

Respiratory system

Points to consider on clinical investigation of medicinal products in the treatment of patients with acute respiratory distress syndrome	CPMP/EWP/504/97
Points to consider on clinical investigation of medicinal products in the treatment of patients with chronic obstructive pulmonary disease (COPD)	CPMP/EWP/562/98
Note for Guidance on the clinical investigation of medicinal products in the treatment of asthma	CPMP/EWP/2922/01
Points to consider on the requirements for clinical documentation for orally inhaled products (OIP).	CPMP/EWP/4151/00*

Reumatology

Medicinal Products (non-steroidal anti-inflamatory compounds) for the treatment of chronic disorders	EudraLex vol. 3C
Points to consider on clinical investigation of medicinal products used in the treatment of osteoarthritis	CPMP/EWP/784/97

Points to Consider on Clinical Investigation of Medicinal Product other than NSAIDs for treatment of rheumatoid arthritis	CPMP/EWP/556/95 rev. 1*

Varia

Points to consider on clinical investigation of medicinal products for the management of Crohn's disease	CPMP/EWP/2284/99
Clinical investigation of corticosteroids intended for use on the skin	EudraLex Vol. 3C
Points to consider on the Evaluation of diagnostic agents	CPMP/EWP/1119/98
Note for guidance on the clinical investigation of medicinal products for the treatment of urinary incontinence	CPMP/EWP/18/01
Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome	CPMP/EWP/785/97

Information on medicinal products

Summary of product characteristics for benzodiazepines as anxiolytics or hypnotics	EudraLex vol. 3B
Summary of products characteristics of angiotensin converting enzyme inhibitors	EudraLex vol. 3B
User leaflet on oral contraceptives	EudraLex vol. 3B
Summary of product characteristics for antimicrobial medicinal products	EudraLex vol. 3B
Summary of product characteristics for antibacterial medicinal products	EudraLex vol. 3B

* New Guidelines.

Module 2.3
Quality Overall Summary - herbal

INTRODUCTION

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.3 Characterisation (name, manufacturer)

For herbal substances and herbal preparations:
A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data, as described in S3.1, should be included.

The QOS should summarise the data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactive contamination, fumigants, etc.

2.3.S.4 Control of Drug Substance (name, manufacturer)

2.3.S.5 Reference Standards of Materials (name, manufacturer)

2.3.S.6 Container Closure System (name, manufacturer)

2.3.S.7 Stability (name, manufacturer)

Module 3
Quality - herbal

Chemical-pharmaceutical and biological information for chemical active substances and biological medicinal products.

NTA, Volume 2B, CTD-Module 3-herbal

Edition July 2003

Scope of the Guideline

3.1 Table of contents of Module 3

3.2 Body of data

3.2.S. DRUG SUBSTANCE[1] (NAME, MANUFACTURER)

3.2.S. 1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the herbal substance should be provided:

- Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable)
- Parts of the plants
- Definition of the herbal substance
- Other names (synonyms mentioned in other Pharmacopoeias)
- Laboratory code

Information on the nomenclature of the herbal preparation should be provided:

- Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable)
- Parts of the plants
- Definition of the herbal preparation
- Ratio of the herbal substance to the herbal preparation
- Extraction solvent(s)
- Other names (synonyms mentioned in other Pharmacopoeias)
- Laboratory code

3.2.S.1.2 Structure (name, manufacturer)

The following information for herbal substance(s) and herbal preparation(s) where applicable, should be provided:

- Physical form
- Description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass).
- Other constituent(s)

[1] For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance

3.2.S.1.3 **General Properties** (name, manufacturer)

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

For herbal substances

The name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate.

For herbal preparations

The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation should be provided, where appropriate.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

For herbal substances
Information should be provided to adequately describe the plant production and plant collection, including:

- Geographical source of medicinal plant
- Cultivation, harvesting, drying and storage conditions
- Batch size

For herbal preparations
Information should be provided to adequately describe the manufacturing process of the herbal preparation, including:

- Description of processing (including flow diagram)
- Solvents, reagents
- Purification stages
- Standardisation
- Batch size

3.2.S.2.3 Control of Materials (name, manufacturer)

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

A brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s) where applicable described in S1 should be discussed, where appropriate.

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

For herbal substances

Information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary, should be provided:

For herbal preparations

Information on the phyto- and physicochemical characterisation, and biological activity if necessary, should be provided:

3.2.S.3.2 Impurities (name, manufacturer)

3.2.S.4 Control of Drug Substance (name, manufacturer)

Data for herbal substance(s) and herbal preparations should be provided.

3.2.S.4.1 Specification (name, manufacturer)

3.2.S.4.2 Analytical Procedures (name, manufacturer)

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

3.2.S.4.4 Batch Analyses (name, manufacturer)

3.2.S.4.5 Justification of Specification (name, manufacturer)

3.2.S.5 Reference Standards or Materials (name, manufacturer)

3.2.S.6 Container Closure System (name, manufacturer)

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

3.2.S.7.3 Stability Data (name, manufacturer)

3.2.P. DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

3.2.P.2 Pharmaceutical Development (name, dosage form)
3.2.P.2.1 Components of the Drug product (name, dosage form)

3.2.P.2.1.1 Drug Substance (name, dosage form)

3.2.P.2.1.2 Excipients (name, dosage form)
3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.2.1 Formulation Development (name, dosage form)

For herbal medicinal products:

A brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the products used in supporting bibliographic data and the product described in P1 should be discussed, where appropriate.

3.2.P.2.2.2 Overages (name, dosage form)

3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

3.2.P.2.4 Container Closure System (name, dosage form)

3.2.P.2.5 Microbiological Attributes (name, dosage form)

3.2.P.2.6 Compatibility (name, dosage form)

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

3.2.P.3.2 Batch Formula (name, dosage form)

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

3.2.P.4.2 Analytical Procedures (name, dosage form)

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

3.2.P.4.4 Justification of Specifications (name, dosage form)

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

3.2.P.4.6 Novel Excipients (name, dosage form)

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

3.2.P.5.2 Analytical Procedures (name, dosage form)

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

3.2.P.5.4 Batch Analyses (name, dosage form)

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

3.2.P.5.6 Justification of Specification(s) (name, dosage form)

3.2.P.6 Reference Standards or Materials (name, dosage form)

3.2.P.7 Container Closure System (name, dosage form)

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

3.2.P.8.3 Stability Data (name, dosage form)

Module 3.2.R –

Regional Information

For EU

Any additional drug substance/active substance and/or drug product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance.

- **Process Validation Scheme for the Drug Product**
- **Medical Device**
- **Certificate(s) of Suitability**
- **Medicinal products containing or using in the manufacturing process materials of animal and/or human origin**

  Compliance with the Annex I to Dir. 2001/83/EC, Part I, Module 2, paragraph 3.2 **(9)**

Module 3.3 – Literature References

Annex to Module 3

(Updated June 2003)

A. List of references to quality guidelines

General Guidelines

Active Substance Guidelines

Medicinal Product Guidelines

B. List of references to biotechnology guidelines

C. List of references to herbal guidelines

Document Title	Number / *version*
Note for Guidance on Quality of Herbal Medicinal Products	**CPMP/QWP/2819/00** EMEA/CVMP/814/00
Note for Guidance on Specifications: Test procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products	**CPMP/QWP/2820/00** EMEA/CVMP/815/00
Note for Guidance on Quality of Water for Pharmaceutical Use	**CPMP/QWP/158/01** EMEA/CVMP/115/01)