

[^{F1}ANNEX IANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS
AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS**Textual Amendments**

- F1** Substituted by [Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use \(Text with EEA relevance\)](#).

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

5. MODULE 5: CLINICAL STUDY REPORTS

5.1. Format and Presentation

The general outline of Module 5 is as follows:

- Table of contents for clinical study reports
- Tabular listing of all clinical studies
- Clinical study reports
 - *Reports of Bio-pharmaceutical Studies*
 - Bio-availability Study Reports
 - Comparative Bio-availability and Bio-equivalence Study Reports
 - In vitro — In vivo Correlation Study Report
 - Reports of Bio-analytical and Analytical Methods
 - *Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials*
 - Plasma Protein Binding Study Reports
 - Reports of Hepatic Metabolism and Interaction Studies
 - Reports of Studies Using Other Human Biomaterials
 - *Reports of Human Pharmacokinetic Studies*
 - Healthy subjects Pharmacokinetics and Initial Tolerability Study Reports
 - Patient Pharmacokinetics and Initial Tolerability Study Reports
 - Intrinsic Factor Pharmacokinetics Study Reports
 - Extrinsic Factor Pharmacokinetics Study Reports
 - Population Pharmacokinetics Study Reports
 - *Reports of Human Pharmacodynamic Studies*
 - Healthy Subject Pharmacodynamic and Pharmacokinetics/Pharmacodynamic Study Reports
 - Patient Pharmacodynamic and Pharmacokinetics/Pharmacodynamic Studies Study Reports
 - *Reports of Efficacy and Safety Studies*
 - Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

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- Study Reports of Uncontrolled Clinical Studies
- Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses
- Other Study Reports
- *Reports of Post-marketing Experience*
- Literature references

5.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

- a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.
- b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmacodynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.
- c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:
 - for at least 15 years after completion or discontinuation of the trial,
 - or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,
 - or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of

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the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used
- audit certificate(s), if available
- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject
- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

e) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

f) The clinical observations shall be summarised for each trial indicating:

- 1) the number and sex of subjects treated;
- 2) the selection and age-distribution of the groups of patients being investigated and the comparative tests;
- 3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;
- 4) where controlled trials were carried out under the above conditions, whether the control group:
 - received no treatment

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- received a placebo
 - received another medicinal product of known effect
 - received treatment other than therapy using medicinal products
- 5) the frequency of observed adverse reactions;
 - 6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;
 - 7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;
 - 8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.
- g) In addition, the investigator shall always indicate his observations on:
- 1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;
 - 2) any interactions that have been observed with other medicinal products administered concomitantly;
 - 3) the criteria determining exclusion of certain patients from the trials;
 - 4) any deaths which occurred during the trial or within the follow-up period.
- h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.
- i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.
- j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.2.1. Reports of bio-pharmaceutics studies

Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.

In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).

5.2.2. Reports of studies pertinent to pharmaco-kinetics using human bio-materials

For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. Reports of human pharmaco-kinetic studies

a) The following pharmaco-kinetic characteristics shall be described:

- absorption (rate and extent),
- distribution,
- metabolism,
- excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.

In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics 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- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. Reports of human pharmaco-dynamic studies

a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:

- the dose-response relationship and its time course,
- justification for the dosage and conditions of administration,
- the mode of action, if possible.

The pharmaco-dynamic action not related to efficacy shall be described.

The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. Reports of efficacy and safety studies

5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

In general, clinical trials shall be done as ‘controlled clinical trials’ if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

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- (1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.
- (2) The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account guidelines published by the Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports shall be provided.

5.2.6. Reports of post-marketing experience

If the medicinal product is already authorised in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.2.7. Case reports forms and individual patient listings

When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.]