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ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Definition of Investigational Medicinal Products (IMPs)

Definition of Non Investigational Medicinal Products (NIMPs)

To be included in
The rules governing medicinal products in the European Union

Volume 10
Clinical Trials
Notice to Applicants

Chapter V Additional Information
Questions and Answers

Investigational Medicinal Product (IMP)

Introduction

To facilitate clinical trials in the case of multi-centre trials carried out in more than one Member States it is necessary to have a common understanding of the definition of an investigational medicinal product. This document presents a definition of investigational medicinal products and non-investigational medicinal products as agreed between the Member States and the Commission.

The definition of an "investigational medicinal product" (IMP) is linked to (a) the definition of a "medicinal product", (b) the intended use of a medicinal product and (c) the definition of a "clinical trial" for the purposes of Directive 2001/20/EC[1]. A clear understanding of the definition of an IMP requires knowledge of the definitions of a medicinal product and of a clinical trial; these two definitions are provided in Annex A. An algorithm and its endnotes, provided in the Notice to applicants Questions and Answers Clinical Trial Documents[2], will help sponsors to determine whether the study is a clinical trial on medicinal product or not.

Directive 2001/20/EC, Article 2 (d), provides the following definition for an IMP:
"a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."

Therefore, to classify a "medicinal product" as an "investigational medicinal product" a sponsor must consider both its intended use and the objectives of the study. For example, if it is to be used as the test substance or reference substance (active comparator or placebo) in a study it would meet the first criteria of an IMP. However, if the study is <u>not</u> intended to discover or verify: (a) its clinical, pharmacological and/or other pharmacodynamic effects or (b) to identify any adverse reactions associated with its use or (c) to study its absorption, distribution, metabolism and excretion; with the objective of ascertaining its safety or efficacy, it would fail the second test. It would therefore not be classified as an IMP. Medicinal products with a marketing authorisation (MA) are classified as IMPs when they are to be used as the test substance or reference substance in a clinical trial. They can be used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or used to gain further information about the authorized form

According to provisions laid down by Directive 2001/20/EC, Directive 2005/28/EC[3] and detailed guidance, some requirements related to these items may be adapted and simplified especially when the IMP is used in accordance with its MA.

Another consequence of the definition of a medicinal product as an IMP is that it must be recorded in the EudraCT database, as stated in the Commission guidance on applications to the competent authority (CT-04-EN)[4].

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[1] OJ L 121 1.5.2001 p.34
[2] Volume 10 Clinical Trials Chapter V
[3] OJ L 91 9.4.2005 p. 13

1. Medicinal products falling outside the definition of IMP

1.1. General guidance

Products which are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to subjects participating in a trial and used in accordance with the protocol. For instance, some clinical trial protocols require the use of medicinal products such as support or rescue/escape medication for preventive, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response.[5]

These medicinal products do not fall within the definition of investigational medicinal products in Directive 2001/20/EC and are called "non-investigational medicinal products" (NIMPs). They may be supplied by the sponsor who provides details of these NIMPs and their proposed use in the trial protocol and ensure that they are of the necessary quality for human use.

It is recommended that a sponsor uses a NIMP with a MA in the Member State concerned for these purposes when possible[6]. When this is not possible, it is recommend that his next choice is a NIMP with a MA in another Member State. In exceptional circumstances a NIMP without a MA in the EU may need to be used. Although these products do not fall within the definition of the IMP, some Member States may treat them as an IMP for the purposes of applying for a clinical trial authorisation if they are not authorized for the indication in the Member State[7].

1.2. Specific guidance

This section provides guidance on some categories of NIMP; it does not cover all types of NIMP.

1.2.1. Rescue medication

Description

These are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.

Rescue medication allows patients to continue in the clinical trial, e.g. placebo controlled clinical trials where a standard treatment is available or dose response

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[4] CT-04-EN, Rev 2 Oct 2005 "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial".

[5] Section 3 CT-04-EN Rev 2 Oct 2005, as in footnote 1.

[6] Section 4.1.7. CT-04-EN Rev 2 Oct 2005, as in footnote 1.

[7] **Rescue medications**: Spain, The Netherlands, Italy consider these products as IMPs if they are not authorised for the indication in the MS; **Challenge agents**: Ireland, Norway, Spain, The Netherlands, Italy, Germany consider these products as IMPs if they are not authorised for the indication in the MS; **Medicines used to assess primary end-points:** Ireland, the Netherlands, Italy, Spain, Sweden, Germany consider these products as IMPs if they are not authorised for the indication in the MS

studies where lower doses might be ineffective. Rescue medications are sometimes called ‘Escape medications’ in protocols. Usually these NIMPs have a MA in the MS and are used according to the authorised conditions. Generally, only those patients assigned to placebo or to an ineffective dose of the treatment will be exposed to rescue medications; this minimises the possibility of interactions with the test medicine.

Examples:

Ineffective treatment

A repeated-dose, randomised, double-blind, placebo-controlled, three-parallel group study performed to evaluate the analgesic efficacy and safety of intravenous acetaminophen as compared with its prodrug (propacetamol) and placebo in patients suffering mild to moderate pain after an orthopaedic surgical operation. Patients were allowed "rescue" patient-controlled intravenous morphine for pain.

Anticipated adverse reactions

A phase III clinical trial trying to assess the efficacy of a new anti-neoplasic IMP. All patients receive a corticoid /antihistamine treatment in order to minimise the appearance of expected adverse reactions;

Anticipated emergency situation

A clinical trial where a new biotechnology product is to be given for the first time to humans. The protocol requires the availability of appropriate medicinal products needed for the treatment of anaphylactic shock.

1.2.2. Challenge agents

Description

This type of product is usually given to trial subjects to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed. They may be substances without a MA, however some have a long tradition of clinical use.

Examples

Bronchoconstriction

The methacholine challenge test may be used in a pharmacodynamic dose-response clinical trial to induce a certain level of bronchospasm in healthy volunteers or in patients with mild asthma in order to measure airway responsiveness and the bronchodilator potential of an IMP.

Skin prick test

Skin prick tests may be used to identify subjects with allergic responses to specific allergens. Dilute solutions are manufactured from extracts of allergens such as pollens, house dust, animal dander and foods. In the skin prick test, a drop of each solution is placed on the person's skin, which is then pricked with a needle. If the person is allergic to one or more substances, s/he has a wheal and flare reaction. This test may be used as part of the inclusion criteria for a clinical trial of a new medicine to control or prevent symptoms from allergic reactions.

Blood pressure

Open-label sensitivity test of blood pressure response to oral tyramine following treatment with an IMP (new MAO inhibitor) in healthy volunteers.

1.2.3. Medicines used to assess primary end-points in the clinical trial

Description

This type of NIMP is given to the subject as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial. They may be substances without a marketing authorisation or have a marketing authorisation but being used in off-labelled indications in the clinical trial.

Examples

Organ function

PET radiopharmaceuticals are administered to a clinical trial population to measure the function of a certain organ before and after the subject has been given an IMP whose effects in this organ are the primary end-point of the clinical trial.

Arterial wall function

Acetylcholine is administered directly in coronary arteries to evaluate coronary endothelium dysfunction. The test is performed at baseline – before the first administration of an IMP, and at the end of the study, after the treatment period.

1.2.4. Concomitant medicinal products systematically prescribed to the study patients

Description

This type of NIMP is given to clinical trial participants as part of their standard care for a condition which is not the indication for which the IMP is being tested, and is therefore not the object of the study.

Example

Symptom relief

Testing a non-oncologic medication in a cancer patient, where the objective of the clinical trial is to assess the analgesic effect of a new opiate product. The study design would test the opiate versus active comparator for pain control, in patients treated for cancer with the same anti-cancer treatment in the two groups. Anti-cancer treatment is not an IMP.

2. Background treatment

2.1. Description

This type of medicinal product is administered to each of the clinical trial subjects, regardless of randomisation group, to treat the indication which is the object of the study. In these trials, a new IMP is given in addition to the background treatment to assess any additional effect of adding an IMP to a medicinal product(s) normally used in standard care. The protocol may require that the test medicine plus the standard care medicine(s) is compared to a placebo or active comparator plus the standard care medicine(s).

The timing of the start of standard care as a background treatment may be different. For instance:

- Subjects may already be taking the standard care medicine(s) when entered into the study, and this treatment would be one of the inclusion criteria; or
- Newly diagnosed subjects may be assigned to the standard care medicines at the same time as they are assigned to the IMP.

The nature of the background medicine(s) will be specified in the protocol e.g. as the standard treatment given according to local clinical practice, by the name of active substances or medicines prescribed depending on patient needs and according to the doctor's judgement.

The standard care medicine(s) for a specific indication (recognised standard of care), or a component of the standard care for a particular medical indication, is based on national and international consensus. When used as a background, the medicine(s) is usually authorised and used within the terms of its MA including the indication being studied.

When background treatment is not used within the terms of its MA but according to a standard of care, it is recommended that the sponsor provides information justifying that it represents the accepted standard of care.

However for some indications the standard care medicine(s) may not have a MA in all of the Member States where the trial is to be conducted. Furthermore, the MA status of the medicinal products involved may vary in different Member States. For instance, a MA may include a particular indication in one Member State and not in others. Moreover, in some specific fields, such as haematology/oncology and paediatric trials, standard of care medicine(s) may not be being used within the terms of a MA.

Background medicine will be considered to be a NIMP in those cases where all the following criteria are met:

- The objective of the trial is not to gain further information about this background treatment. In this context, the protocol would not address any specific question about the background treatment, except that it is administered to each of the clinical trial subjects in association with the tested/reference product;
- The protocol defines the background medicine(s) without requiring specific brands to be used ; and
- The medicines are prescribed as they would be for standard care of the patients, and therefore they are authorised in all Member States participating in the clinical trial.

2.2. Examples

Standard treatment

Development of new medicinal products for HIV cannot be tested against a placebo control without the patient being on a standard established medicine(s). The protocol might require that the test compound be compared to an active comparator and/or placebo; each of these would be an IMP. The standard established medicine(s), if it is used within the terms of its marketing

authorisation and if the protocol does not raise any specific issue on this medicine(s) would not be an IMP.

Development of a new medicinal product for HIV patients who need prophylaxis against cytomegalovirus (CMV) is likely to include patients on standard of care medicine(s) for their primary disease (e.g. antiretroviral medicines), which would not be IMPs. The protocol might require that the test product for CMV prophylaxis be compared with an active comparator and/or a placebo, each of which would be an IMP. Clinical trial patients would also be on a multi-medicinal products 'standard of care' regimen. These standard of care medicinal products would not be IMPs.

No standard treatment

Development of a new treatment for mesothelioma is likely to include patients already on chemotherapy medicine(s). However there is no standard treatment for mesothelioma. Recent trials compared the combination of Pemetrexed with Cisplatin versus Cisplatin alone. In this case the background treatment Cisplatin, which is not authorised for mesothelioma, was also the comparator. Therefore both Premetrexed and Cisplatin would be IMPs.

Partly defined standard treatment

This second oncology example[8] refers to combination treatments that are all approved for the treatment of the disease to be investigated but are not completely defined in the protocol. Development of a new indication for Herceptin in women with HER2 positive breast cancer recently compared Herceptin versus observation in patients who had received at least four cycles of neoadjuvent or adjuvent chemotherapy and were allowed concurrent hormonal adjuvent therapy. In this case Herceptin would be considered an IMP and the adjuvent therapy would be NIMPs.

3. Requirements for Non Investigational Medicinal Products (NIMPs)

It is recommended that medicinal products with a MA in the Member States concerned are used as NIMPs when possible. When this is not possible, it is recommended that the next choice is medicinal products with a MA in another MS.

3.1. Providing information related to the NIMPs to the competent authority

It is recommended that the sponsor provides details of the NIMP and their proposed use in the trial protocol.[9] A NIMP dossier should be provided in accordance with the Commission guidance on applications to the competent authority (CT-04-EN)[10].

The sponsor is responsible for ensuring that these products are the ones notified in the clinical trial authorisation and the protocol.

3.2. Manufacturing and packaging of NIMPs; Traceability of the NIMPs and compliance assessment

[8] Trastuzumab after adjuvent chemotherapy in HER2-positive breast cancer. Piccart-Gebhart MJ et al., N Engl J Med 2005 Oct 20;353(16)1659-72

[9] Section 3(4), CT-04-EN Rev 2 Oct 2005, as in footnote 1

[10] Section 4.1.7. CT-04-EN Rev 2 Oct 2005, as in footnote 1

As NIMPs do not fall within the definition of investigational medicinal products, provisions of Directive 2001/20/EC Article 13 and 14 do not apply to these products. However, when the NIMPs do not have any MA in the EU, it is recommended that the sponsor ensure that they are of appropriate quality for the purposes of the trial taking into account, among other things, the source of the materials and any repackaging.

The sponsor is responsible for implementing a system to ensure that the trial is conducted and data are generated in accordance with the principles of Good Clinical Practice. To comply with these principles, a trial has to be conducted according to the protocol and all clinical trial information should be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified[11]. In this context, the sponsor should implement a system allowing traceability of medicinal products using:

- A similar system to that required for IMPs; or
- An alternative system which allows adequate reconstruction of NIMP movements and administration, taking into account the purpose of the trial and patients safety. It has at least include a procedure, established with the investigator and if applicable, with the hospital pharmacy, to record which patients received which NIMPs during the trial with an evaluation of the compliance.

3.3. Adverse drug reactions related to NIMPs

Requirements

The sponsor is responsible for the ongoing safety evaluation of the clinical trial subjects. This task also involves serious events related to NIMPs.

The requirements to notify serious adverse reactions (SAR) set out in Article 17 of Directive 2001/20/EC do not apply to a NIMPs because it is outside the definition of an investigational medicinal product (Article 2(d) of Directive 2001/20/EC) and an adverse reaction as defined by Article 2(n) only applies to an investigational medicinal product.

Investigator's Responsibilities

The requirements for the investigator to notify adverse events set out in Article 16 of Directive 2001/20/EC are not specifically related to investigational medicinal products. Investigators should therefore notify the sponsor of serious adverse events in accordance with Article 16. In addition to this general requirement Article 10(b) of the Directive requires that when new events occur that are likely to affect safety of the subjects the investigator must take appropriate urgent safety measures to protect the patients against immediate hazard. Requirements of Articles 16 and 10(b) of Directive 2001/20/EC apply for events related to an NIMP.

Sponsor's Responsibilities

Expedited reporting

Article 16(4) of Directive 2001/20/EC requires the sponsor to keep detailed records of all adverse events which are reported to him by the investigator(s).

[11] Commission Directive 2005/28/EC, Art. 4 and 5, and GCP (CPMP/ICH/135/95) guideline, section 2

The requirement to take appropriate urgent safety measures described in the paragraph above also applies to the sponsor. He is required to inform the competent authorities of the Member State concerned and the Ethics Committee forthwith of those new events and the measures taken.

If the medicinal product adverse reaction is suspected to be linked to an interaction between an NIMP and an IMP the sponsor should report it as a suspected serious unexpected adverse reaction due to an interaction with the IMP according to Article 17 of Directive 2001/20/EC. When an interaction is not suspected, if the NIMP has a MA, the investigator or sponsor should report serious adverse drug reactions due to NIMPs in accordance with pharmacovigilance provisions of Directive 2001/83/EC as amended.

If the medicinal product reaction due to the NIMP is likely to affect the safety of the trial subjects, the sponsor should report it to each competent authority and ethics committee concerned in accordance with article 10(b) of Directive 2001/20/EC and section 5.1.1.2 of the detailed guidance on the collection, verification and presentation of adverse reaction reports[12].

Annual safety report

Section 5.2 of Guidance CT3, April 2006[13], requires sponsors to submit, once a year or on request, a safety report describing concisely all relevant new findings related to the safety of the subjects in the concerned clinical trial throughout the reporting period. Relevant new safety findings related to NIMPs including suspected serious unexpected adverse reactions and any other relevant information occurring in the reporting period should be described in part 1 of the annual safety report (Analysis of the subjects' safety). However serious adverse reactions only related to NIMPs should not be described in parts 2 and 3 of the report.

[12] Section 5, Guidance CT3, April 2006 as in footnote 11
[13] Section 5.2.1, Guidance CT3, April 2006 as in footnote 11.

Annex A

General definitions useful for this guidance

Medicinal Product

Article 1.1 of Directive 2004/27/EC provides the definition of "medicinal product" which applies for the purposes of Directive 2001/20/EC.
It is:
(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

The definition includes somatic cell therapy medicinal products which use somatic living cells of human (or animal) origin, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect (in humans) through metabolic, pharmacological and immunological means. It does not include whole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process.

Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and it is presented for a medicinal purpose.

Clinical Trial

Article 2 (c) of Directive 2001/20/EC defines a clinical trial as:

> a) *clinical trial*: any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.
> This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State.
>
> (c) *non-interventional trial:* a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.