EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials

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

Volume 10
Clinical Trials
Notice to Applicants

Chapter V Additional Information

1. Introduction

To facilitate the conduct of clinical trials in the member States of the European Union, especially multi-centre clinical trials carried out in more than one member State it is necessary to have a common understanding of the definition of an investigational medicinal product.

This document intends to clarify and provide additional guidance on the definition of investigational medicinal products and to provide specific guidance about the use of non-investigational medicinal products, in accordance with the applicable EU legislation.

This document complements the "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"[1] and the "Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use".[2]

2. Investigational Medicinal Products (IMP)

The definition of an "investigational medicinal product" (IMP) is provided in Directive 2001/20/EC, Article 2 (d), as "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."

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, provided they are used or assembled (formulated or packaged) in a way different from the authorised form, or used for an unauthorised indication, or used to gain further information about the authorised form. On this basis, provided that the requirement(s) are met, reference products used as comparators should be considered as IMPs.

3. Other Medicinal products used in clinical trials

3.1. General guidance

Products which are not IMPs as referred to in Art. 2(d) of Directive 2001/20/EC 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 concomitant 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.

These medicinal products do not fall within the definition of investigational medicinal products in Directive 2001/20/EC and can be referred to as "non-investigational medicinal products" (NIMPs).

[1] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/11_ca_14-2005.pdf
[2] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/12_ec_guideline_20060216.pdf

They may be supplied by the sponsor who provides details of these NIMPs and their proposed use in the trial protocol and ensures that they are of the necessary quality for human use. NIMP may be supplied by the investigator site.

It is recommended that a sponsor uses NIMPs with marketing authorisations (MA) valid in the Member State concerned, either authorised at Community or national level. If this is not possible, it is recommended that a NIMP with a MA in another Member State is used.

Medicinal products that do not have a marketing authorisation, but prepared in accordance with a magistral formula, i.e. prepared in a pharmacy in accordance with a medical prescription for an individual patient, and medicinal products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia[3] and intended to be supplied directly to the patients served by the pharmacy in question, i.e. officinal formula, as referred to in Article 3(1) and (2) of Directive 2001/83/EC may also be used as NIMPs in a clinical trial.

3.2. Requirements for Non Investigational Medicinal Products (NIMPs)

Medicinal products with a marketing authorisation valid throughout the Community or in one or more Member State(s) and not covered by the definition of an IMP are governed by the requirements of Directive 2001/83/EC ensuring the quality, safety and efficacy of the product, which guarantees the safety of the patients with regard to the use of the products with MA. In particular the GMP requirements provided by Title IV of Directive 2001/83/EC ensure the quality of the products.

The safeguarding of the clinical trial subject, in accordance with Article 3 and the objectives of the Directive is ensured inter alia by guaranteeing the quality and safety of the products and substances used in the trial. As NIMPs do not fall within the definition of investigational medicinal products, Articles 13 and 14 of Directive 2001/20/EC are not directly applicable. However, when NIMPs do not have a MA in the EEA, appropriate GMP requirements foreseen for the safety of the patients should still be applied and the sponsor should ensure that NIMPs are of appropriate quality for the purposes of the trial, taking into account, among other things, the source of the raw materials and any repackaging. To meet the requirements of Articles 3(2) and as referred to in Article 6(3) of the Directive relating to protection of the trial subject, the same level of quality and safety should be ensured for the NIMPs as for the IMPs used in the trials.

This requirement will be fulfilled by applying for these NIMPs, the same requirements as provided for the IMPs, in particular, the standards as provided for in Title IV of Directive 2001/83/EC and the requirements established under Articles 13(3) and 15 of the Directive should be applied.

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

[3] For reference to acceptable pharmacopoeial monographs see section 1.5 General Considerations — "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" CHMP/QWP/18540/2004 final which is part of Eudralex Volume 10 of Rules Governing Medicinal Products in the European Union

and verified. In this context, the sponsor should implement a system allowing traceability of medicinal products which allows adequate reconstruction of NIMP movements and administration taking into account the purpose of the trial and trial subjects' safety. It has at least to 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. Information related to the NIMPs to be provided to the competent authority

The sponsor should provide details of the NIMP and their proposed use in the trial protocol. Information on the NIMP should be provided in accordance with the Commission guidance on applications to the competent authority (ENTR CT 1).

3.4. Adverse drug reactions related to NIMPs

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

Article 10(b) of Directive 2001/20/EC requires that when new events occur that are likely to affect safety of the subjects the sponsor and the investigator must take appropriate urgent safety measures to protect the subjects against immediate hazard.

Article 16 of Directive 2001/20/EC requires the investigator to notify to the sponsor any adverse events occurring in the clinical trial which may be related to the use of IMPs or NIMPs. It also requires the sponsor to keep detailed records of all adverse events which are reported to him by the investigator(s).

Requirements of Articles 10(b) and 16 of Directive 2001/20/ECalso apply in relation to NIMPs and include adverse events/reactions occurring with the use of these products.

If the adverse reaction is suspected to be linked to an interaction between a NIMP and an IMP, and is serious and unexpected, the sponsor should report it as a suspected unexpected serious adverse reaction (SUSAR) due to the interaction with the IMP according to Article 17 of Directive 2001/20/EC.

If an adverse reaction (serious and unexpected) is suspected and might be linked to either a NIMP or an IMP and cannot be attributed to only one of these, then the sponsor should report it as a SUSAR in accordance with Article 17 of Directive 2001/20/EC.

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[4].

[4] [4] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21susar_rev2_2006_04_11.pdf

ANNEX

This section provides guidance on some categories of medicinal products which are normally used in clinical trials as non-investigational medicinal products (NIMPs).

1. Rescue medication

Description

Rescue medications 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 receive effective treatment, e.g. placebo controlled clinical trials where a standard treatment is available or dose response 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. *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.

2. Challenge agents

Description

Challenge agents are 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:

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, he/she 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.

3. Medicinal products used to assess 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.

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.

4. Concomitant medicinal products systematically prescribed to the study patients

Description

This type of NIMP is given to clinical trial participants as required in the protocol 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, regardless of the trial.

5. Background treatment

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. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared to an active comparator or to placebo plus background treatment.

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 medicinal products 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.

Examples

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 medicinal products).

In oncology, patients often receive combination treatments. These may all be approved for the treatment of the disease to be investigated but may not be completely defined in the protocol. For example the development of a new indication for a medicine used in women with breast cancer recently compared that medicine versus observation in patients who had received, regardless of trial, at least four cycles of neoadjuvant or adjuvant chemotherapy and were allowed concurrent hormonal adjuvant therapy. In this case that medicine would be considered an IMP and the neoadjuvant or adjuvant chemotherapy and hormonal therapy products would be NIMPs.