
# GUIDANCE NOTES ON GOOD CLINICAL PRACTICE

# CLINICAL TRIALS APPLICATIONS AND NOTIFICATIONS TO THE MEDICINES AUTHORITY, MALTA

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# 1. SCOPE AND PROVISIONS

These guidance notes have been prepared in order to help applicants when submitting applications and notifications for clinical trials to the Medicines Authority. The Maltese legal framework for this process is set out in the *Clinical Trials Regulations, 2004* (LN 490). This may be accessed on: http://www.doi.gov.mt/EN/legalnotices/2004/11/LN490.pdf. The European legal framework for this process is set out in *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*. This may be accessed on: https://eudract.ema.europa.eu/.

The Medicines Authority reserves the right to amend the text of the guidance notes periodically and interested parties may be required to apply such amendments as deemed necessary by the Medicines Authority.

The application form should be submitted in English. Documentation attached to the application should be submitted in English and/or Maltese.

# 2. DEFINITIONS

***Applicant***

The legal applicant i.e. sponsor or person / organisation authorized by the sponsor or legal representative of the sponsor.

***Commission***

The Commission in accordance with Council Decision 1999/468/EC of 28th June, 1999.

***Health Ethics Committee***

An independent body, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to recruit and inform trial subjects and obtain their informed consent.

***Member State***

A State which is a member of the European Union and shall also include Iceland, Norway and Liechtenstein.

***The Community***

The European Community and the European Economic Area.

***Transmissible Spongiform Encephalopathies Certificate (TSE certificate)***

TSE certificate of suitability issued by the European Directorate for the Quality of Medicines (EDQM).

# 3. INTRODUCTION TO THE REGULATION OF CLINICAL TRIALS

No person shall start a clinical trial in Malta unless the Health Ethics Committee has issued a favorable opinion and the Licensing Authority has authorized it. In order to obtain such an authorisation from the Medicines Authority to start a clinical trial an application shall be submitted to the Medicines Authority.

The *Clinical Trials Regulations, 2004* regulate the conduct of interventional clinical trials, including multi-centre trials, in Malta on human subjects involving medicinal products as defined under the Medicines Act, 2003 and its amendments and in particular relating to the implementation of good clinical practice.

The regulations include both commercial and non-commercial trials. The regulations do not refer to foods, cosmetics or medical devices. Obsolete or repetitive tests cannot be carried out.

# 4. EUDRA CT DATABASE

EudraCT is a database of all interventional clinical trials of medicinal products occurring in the Community on or after 1 May 2004, in accordance with *Directive 2001/20/EC* and the Maltese *Clinical Trials Regulations, 2004*. The database itself is confidential and accessible only to the Competent Authorities of the Member States, the European Medicines Agency and the Commission. However, a sponsor portal is available which gives the sponsor / applicant access to the EudraCT application, amendment forms and end of trial forms, as well as access to supporting documentation.

## 4.1. ENTERING DATA IN EUDRACT DATABASE

Details pasted from certain computer sources (for example, Word documents) are not guaranteed to be correctly displayed in the data fields of the EudraCT database particularly where a graphic or symbol character set is used. Reproduction will depend on the character set used. If the applicant is in doubt, he should check the information entered in the EudraCT database.

The system allows the sponsor's protocol code number to be entered in the normal format used by the sponsor. The sponsor's protocol code number is stored and displayed as entered. It is also stored in lower case, without any spaces, to simplify the comparison of these code numbers by the system in order to check for duplicates. Consequently neither the case of a character nor spaces can be used to convey meaning. If your format uses hyphens or / please ensure that these are always used consistently. If possible encourage your organisation to adopt a simple alphanumeric format without other characters.

# 5. CLINICAL TRIAL APPLICATIONS

An authorisation of a clinical trial granted by the Medicines Authority will only be valid for a particular clinical trial conducted in Malta. This authorisation does not imply approval of the development programme of the tested investigational medicinal product (IMP).

When an applicant submits an application for a clinical trial, he must fill in the application form: *Request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the community.*

The application should be prepared in accordance with the European Commission's *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*. The application form and guidance notes may be accessed on: *https://eudract.ema.europa.eu* and *http://ec.europa.eu/health/documents/eudralex/vol-10/*

The completed form should be submitted with the required documentation (annex 14 of these guidance notes).

Applicants should make all submissions for initial applications, substantial amendments, annual safety reports, responses to remarks in an acceptance letter, or responses to letters giving grounds for non-approval, by providing electronic documents on disk.

The following disk formats are acceptable:

CD-ROM
DVD-ROM

Labelling disks

Each disk should be labelled in the following manner:

EudraCT number

Description of contents

- Initial Application
- Response to Remarks from an Initial Application
- Notification of a Substantial Amendment
- Response to Remarks from a Substantial Amendment
- Notification of End of Trial
- Annual Safety Report

- End of Study Report
- SUSAR
- Company name
- Date sent

The disk may be printed or labelled with an adhesive paper label or a permanent marker pen.

Posting disks

All disks should be sent to the address below:

Clinical Trials Unit
Medicines Authority
203 Level 3, Rue D'Argens
Gzira GZR 1368
Malta
Europe

## 5.1 SUBMITTING THE CLINICAL TRIAL APPLICATION

When preparing the documents to be submitted with the initial clinical trial application, the applicant should follow Annex 12 of these guidance notes

Before submitting the application the applicant must make sure that the full dataset has been filled in.

The XML file (electronic version of the application form) should preferably be named with the EudraCT number of the clinical trial. To avoid errors the applicant should copy and paste correctly the number instead of re-entering the digits one by one.

## 5.2 VALIDATION OF THE DOCUMENTATION RECEIVED

The documentation received will be subject to a validation check in order to ensure that all information requested is submitted correctly. If additional information is required, the applicant is informed accordingly and the validation period continues after the requested documentation is submitted correctly.

## 5.3 ASSESSMENT OF THE DOCUMENTATION RECEIVED

Assessment of the documentation will start after the validation review process has taken place. The applicable assessment timeframes mentioned in the *Clinical Trials Regulations, 2004* would apply upon commencement of the assessment.

The Medicines Authority reserves the right to reject the application and gives the reasons

in writing for so doing. In this case, the applicant may appeal only once and within twenty (20) calendar days of the notification of the negative decision from the Medicines Authority. Further documentation may be presented during this appeal.

# 6. AMENDMENTS

After a clinical trial has started, no person shall implement a substantial amendment (except in the case of urgent safety amendments, as specified below) in Malta unless, where applicable, this has been authorised by the Medicines Authority and has also obtained a favourable opinion from the Health Ethics Committee.

When submitting an amendment, the application form Notification of a substantial amendment to a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the community needs to be filled.

Substantial amendment forms together with the relevant documentation should be submitted to the Medicines Authority according to the European Commission's *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.* The application form and guidance notes may be accessed on: https://eudract.ema.europa.eu. Any changes to the initial application should be reflected by a revised XML file being submitted to the Medicines Authority.

Any amendments should be clearly identifiable.

Pursuant to Legal Notice 490 of 2004 (Malta), substantial amendments (SA) are understood to be those initiated by the clinical trial sponsor.

Article 10 of the Maltese Legal Notice 490 of 2004, defines substantial amendments as those having a significant impact on any aspect of the clinical trial, namely on the followings :

- the protection of clinical trial participants (inclusive of the conduct or management of the trial), including safety aspects (inclusive of the quality or safety of any product used in the trial (investigational medicinal products and any other products used for the purpose of the research),
- the scientific value of the trial (inclusive of the interpretation of the clinical trial documentation (e.g. the protocol, the investigator's brochure or the clinical trial authorisation form).

An amendment is to be regarded as "substantial" when one or more of the criteria listed above are met.

## 6.1 NON-SUBSTANTIAL AMENDMENTS

Non-substantial amendments (NSA) do not require notification to the Medicines Authority (neither for authorisation nor form information). They should, however, be documented by the sponsor and be made available to the Medicines Authority on request.

6.2 SUBSTANTIAL AMENDMENTS

The following are examples of substantial amendments that need to be submitted to the Medicines Authority for approval. This list is not inclusive and does not preclude the submission of substantial amendments at the sponsor's initiative.

## I Amendments to the general nature and management of the trial

I.1 Clinical trial Identification

- Change to the identification of the clinical trial specified in section A of the CTA application form(e.g. title of the trial, sponsor's protocol code number )

I.2 Identification of the sponsor or of his legal representative

- Change of sponsor
- Change of legal representative of the sponsor
- Change of name / contact details of the contact person designated by the sponsor or his legal representative

I.3 Applicant Identification

- Change of applicant SAI
- Change of name / contact details of the contact person designated by the applicant

I.4 Investigational Medicinal Product(s) (IMP) Identification

- Change of name / code name of the IMP
- Addition of the INN of the IMP

I.5 General information on the clinical trial

- Change in clinical trial phase

I.6 Clinical trial sites / Investigators

- Change of coordinating investigator or principal investigator in an existing site
- Addition or withdrawal of a research site on gene therapy or cell therapy IMP(s)
- Addition or withdrawal of a research site with IMP(s) other than gene therapy or cell therapy

I.7 Technical Equipment / Service provider(s)

- Changes relative to technical equipment
- Addition of technical equipment
- Change of service provider
- Change in transfer of trial related duties

I.8 Importer

- Change/addition of an importer responsible for the certification of the finished product in the EU

- Change/addition of an importer not responsible for the certification of the finished product in the EU

I.9 Clinical trial participants

- Change in planned number of subjects to be included

I.10 Other changes

- Change of insurance company

I.11 Duration of the clinical trial

- Change to the duration of the study, without change to the duration of exposure to the IMP nor to the duration of treatment with the IMP, but with change to the monitoring of the participants
- Change to the duration of the study, without change to the duration of exposure to the IMP nor to the duration of treatment by the IMP , without change to the monitoring of the participants

## II Amendments related to the quality of the active substance

II.1.1 Manufacturing process for active substance of biological origin

- Change of manufacturer and/or change to the manufacturing process, and/or size of the batch and/or analytical method(s) for the active substance, that may have a significant impact on the safety of the CT participants

II.1.2 Manufacturing process for active substance of chemical origin

- Changes in the manufacturing process resulting in the presence or discover of new impurities

II.2.1 Manufacture of the finished product

- Change of manufacturer or formulation, and/or change in the manufacturing process, and/or the size of the batch, and/or the analytical method(s), and/or the site of primary packaging for the finished product, that may have a significant impact on the safety of the CT participants

II.2.2 Manufacture of the placebo

- Change of formulation likely to have a significant impact on the safety of the CT participants

II.2.3 Stability of the finished product or placebo

- Restriction of the storage conditions motivated by a safety issue

II.2.4 Packaging and labelling of the IMP (including packaging of the placebo)

- Change of IMP dispensing system
- Change of packaging of an IMP, where the IMP is a gene therapy or cell therapy drug

II.2.5 Other modifications related to the quality of the IMP or of the placebo

- Withdrawal or modification of a filter to be placed on the perfusion line upon administration of the drug

II.3 Amendments in viral safety data

- Modification to data presented in the viral safety

## III Amendments related to the non-clinical part of the documentation submitted

- Change to the protocol following a new non-clinical event SAA Impact on risk/benefit assessment of the clinical trial
- New non-clinical data likely to have a significant impact on the safety of participants and/or on the protocol of the trial
- Modifications made to the non-clinical data presented in the investigator's brochure having a significant impact:
    - on the safety of patients,
    - and/or on the CT protocol,

## IV Amendments related to the clinical part of the documentation submitted

IV.1 Objectives of the trial / Endpoints / Design of the trial

- Modification to the main objective of the trial SAA
- Addition of an interventional ancillary study e.g. pharmacokinetics or pharmacogenetics sub-study.
- Change to the primary endpoint and/or a secondary endpoint likely to have a significant impact on the safety of CT participants e.g. addition of an invasive test
- Change to the primary endpoint and/or a secondary endpoint without impact on the safety of CT participants
- Change to the design of the trial (e.g. addition of an arm / addition of a placebo group)

IV.3 Selection of trial participants

- Change to the inclusion / non-inclusion criteria (including the age of the participants)
- Extension to the period of recruitment with change to the duration of the clinical trial

IV.4 Treatment(s) administered

- Change in the mode of administration of the IMPs
- Change of dose
- Addition of new dose ranges
- Change in the duration of exposure to the IMP

- Change of comparator
- Modification to the list of concomitant treatments prohibited / authorised

IV.5 Monitoring of clinical trial participants

- Change to the monitoring

IV.6 Monitoring of the clinical trial

- Addition or withdrawal of an independent data monitoring committee
- Change in the independent data monitoring committee

IV.7 Changes to the investigator's brochure

- Modifications to the clinical data presented in the investigator's brochure likely to have an impact on :
    - the safety of the CT participants,
    - and/or the CT protocol,
    - and/or the assessment of the expectedness of a suspected serious adverse effect (where the IB is the reference document).

IV.8 Other changes to the protocol

- Temporary halt of a clinical trial
- Restart of the clinical trial after a temporary halt
- New clinical safety data relative to the IMP(s), reported from a clinical trial or not, likely to have a significant impact on the safety of the participants and/or on the trial protocol
- New clinical safety data relative to the IMP(s), reported from a clinical trial or not, without impact on the safety of the participants and/or on the trial protocol
- Change in the definition of the end of trial

V Specific cases

- Modifications to the list of investigators
- Modifications to the investigators brochure

## 6.3 VALIDATION OF THE DOCUMENTATION RECEIVED

The documentation received will be subject to a validation check in order to ensure that all information requested is submitted correctly. If additional information is required, the applicant is informed accordingly and the validation period continues after the requested documentation is submitted correctly.

## 6.4 ASSESSMENT OF THE DOCUMENTATION RECEIVED

Assessment of the documentation starts after the validation review process has taken place. The amendment is assessed within a maximum of thirty-five (35) calendar days. During the assessment period of medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms, if the Medicines Authority consults a group or committee the time of response could be extended. In this case the Medicines Authority notifies the sponsor of the duration of the extension.
If further documentation is requested, the applicant is informed accordingly and a clock-stop applies until the required documentation is received. Assessment will resume after a satisfactory response is supplied by the applicant. The applicant is notified on the decision of the Medicines Authority.
The Medicines Authority reserves the right to reject the application and gives the reasons in writing for so doing. In this case, the applicant may appeal only once and within twenty (20) calendar days of the notification from the Medicines Authority. Further documentation may be presented during this appeal.

In the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the IMP where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. These safety measures may be taken without prior authorisation from the Medicines Authority. The sponsor shall communicate to the Medicines Authority the new events, the measures taken and their plan for future action as soon as possible. This should be by telephone in the first place followed by a written report. The written report should be submitted within eight (8) calendar days of the decision (except in the case were the urgent safety amendment involves the premature termination of a clinical trial, where notification should be made within fifteen (15) days). No fee will be attributable in this case.

If the Medicines Authority is notified of any amendments that are relevant to the Health Ethics Committee only and these do not require assessment by the Medicines Authority, no fee will be attributable to the Medicines Authority.

# 7. END OF CLINICAL TRIALS

End of trial notifications should be made using the *Notification of the end of a clinical trial of a medicine for human use to the competent authority and the ethics committee.*

The end of trial form together with any documentation, where applicable, should be made according to the European Commission's *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.* The end of trial form and guidance notes may be accessed on: https://eudract.ema.europa.eu.

# 8 CONTROL OF CLINICAL TRIALS – INSPECTION

The Medicines Authority carries out, on a risk based approach, a number of inspections for clinical trials of medicinal products in Malta. The inspections are partly performed by visiting the doctors carrying out the clinical part of trials, and partly by visiting the companies that are partially or entirely responsible for managing the trials, depending on the particular clinical trial. In addition, inspections can be made by visits to other parties involved in a trial, such as hospital pharmacies and laboratories.

The purpose of the inspections is to control whether the clinical trials are carried out in compliance with Maltese legislation and the authorised trial protocol. Trials of medicinal products must be carried out in accordance with the international code on good clinical practice. Therefore, it is also controlled whether this code of practice is complied with.

The inspections are an attempt to ensure the credibility of the data registered (what does the trial show?) as well as the safety for the trial subjects participating.

The selection of trials for inspection can cover all types of trials to the extent possible. This means the different phases (phases I-IV), single and multi-centre trials, hospitals and general practices or other specialist practices as well as the different medical specialties.

The Medicines Authority can exchange information about the inspections with other relevant authorities upon request and with the sponsors as a procedure.

## 9. CLINICAL TRIALS AND ADR REPORTING (SUSARS)

The legal obligations of the sponsors of clinical trials are specified in Directive 2001/20/EC and the Clinical Trials Regulations 2004 (Legal Notice 490 of 2004). Further guidance on the requirements of sponsors and investigators is outlined in the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" issued by the European Commission. This guidance can be obtained from the following website:

*http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm*

Additional guidance on SUSARs and how to report SUSARs to the Medicines Authority are available in The Medicines Authority's Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations & Adverse Drug Reaction (ADR) Reporting Requirements for Medicinal Products for Human Use. This guidance can be obtained from the following website:

http://www.medicinesauthority.gov.mt/pub/Guidance%20Notes%20to%20MAHs%20re%20PhV%20obligations.pdf

## 10. FEES

Current Fees payable to the Medicines Authority for Clinical Trials are available in Legal

Notice 315 of 2006: Marketing Authorisation (Fees) Regulations, 2006 and Pages 194-199 of Legal Notice 427 of 2007 - Fees in Euros.

Appropriate proof of payment should always be attached with the application. Payment of the relevant fee should be made at:

**Bank Details:** HSBC 198, The Strand, Gżira, GŻR 03
**Account Name:** MEDICINES AUTHORITY
**Account Number:** 039011176002
**IBAN:** MT78 MMEB 44392 0000000 39011176002
**Swift Code:** MMEBMTMT

When effecting the payment the amount should be remitted in full, net of all bank charges.

Whenever a payment is effected in respect of an application which is submitted to the Medicines Authority, the following details need to be submitted to Ms. Analisa Buttigieg on analisa.buttigieg@gov.mt:

1. The name of the company effecting payment
2. The name of the company on behalf of which the payment is effected (when applicable).
3. The amount paid.
4. Date of payment.
5. Type of application.

This information needs to be submitted on the date that the payment is effected.

# 11. CONTACT DETAILS FOR FURTHER INFORMATION

Applications and notifications should be submitted to:

Clinical Trials Unit

Medicines Authority
203 Level 3, Rue D'Argens,
Gżira, GZR 1368
Malta
Europe

Tel: (+00356) 23439000
Fax: (+00356) 23439161
Email: info.mru@gov.mt

# 12. IMPORTANT LINKS

1. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.* Accessed on: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf.

2. *Clinical Trials Regulations, 2004 (LN 490).* Accessed on: http://www.doi.gov.mt/EN/legalnotices/2004/11/LN490.pdf.

3. *Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.* Accessed on: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf.

4. Good Clinical Practice and Requirements for Manufacturing or Import Authorisation of Investigational Medicinal Products (Human Use) Regulations, 2006 (LN 119). Accessed on: http://www.doi.gov.mt/EN/legalnotices/2006/05/LN119.pdf.

5. *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.* Accessed on: https://eudract.ema.europa.eu.

6. *Request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the community.* Accessed on: https://eudract.ema.europa.eu.

7. *Notification of a substantial amendment to a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the community.* Accessed on: *http://eudract.emea.europa.eu.*

8. *Notification of the end of a clinical trial of a medicine for human use to the competent authority and the ethics committee.* Accessed on: https://eudract.ema.europa.eu.

9. *The check list of the information appended to the application* (check list J). Accessed on: https://eudract.ema.europa.eu.

10. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use should be followed. Accessed on: http://www.ich.org. Of particular relevance is the *Note for guidance on good clinical practice* (CPMP/ICH/135/95).

11. Guidance on Pharmacovigilance obligations inclusive of SUSARs: http://www.medicinesauthority.gov.mt/pub/Guidance%20Notes%20to%20MAHs%20re%20PhV%20obligations.pdf

# 13 REVISION HISTORY

| Issue | Effective date | Reason for revision |
|---|---|---|
| GL4.01 | February 2004 | First Issue of the requirements to submit a clinical trial application only to the Medicines Authority |
| GL3.01 | January 2005 | First Issue of the guidance notes for submitting Clinical trial applications |
| GC1.02 | July 2006 | Guideline GL4.01 and GL3.01 are compiled into one guideline to cover the submission of clinical trial applications and amendments |
| GC1.03 | September 2007 | Major update to Annex 12 to include three columns of information and to the requirements of Annex 12. The requirements are harmonized with the requests of other EU Clinical Trial Units. Bank payment details have been updated. The acceptance of an application form on electronic media only is acceptable to submit a clinical trial application/amendment. |
| GC1.04 | November 2007 | Typographical mistakes in Annex 12 have been amended |
| GC1.05 | July 2008 | Information on fees to be paid in Euros is added. |
| GC1.06 | August 2008 | Minor updates to Annex 12; including update to contact details of the Medicines Authority. |
| GC1.07 | November 2009 | A new section has been added with respect to Non-substantial and substantial amendments; Minor changes have been made to Annex 12, Annex 13 has been added |
| GC1.08 | March 2010 | A new section has been added with respect to Clinical Trial Inspections carried out by the Medicines Authority; A revision history of the guideline has been added; Annex 12 has been updated to include the requirements of Annex 13. |
| GC1.09 | April 2010 | A minor addition to Annex 12 has been added regarding a letter from head of trial site stating his/her awareness of the clinical trial to be conducted at the site following an approval of the clinical trial by the Medicines Authority. |
| GC1.10 | September 2010 | A new section has been added with respect to Applicant's obligations on Adverse Drug Reaction Reporting inclusive of SUSARs; Annex 12 has been updated and renamed Annex 13. The revision history of the guideline has been updated to reflect these changes; |

# 14. REQUIREMENTS BY MALTA

**MALTA Validation Requirements**

This annex should be filled in, printed, and submitted with the relevant documentation.

1 soft copy **(on electronic storage media)** of the following documents are required for submission of an application:

| | Supplied | Version | Date |
|---|---|---|---|
| Covering Letter | | | |
| Filled EU application form for a request to conduct a clinical trial or amendment in XML and PDF format | | | |
| Filled validation form (GC 1.10 Section 14 ) | | | |
| Requirements of GC1.10 section 15 have been fulfilled<br><br>Copy of email sent to *analisa.buttigieg@gov.mt* with the details of payment<br>1. The name of the company effecting payment<br>2. The name of the company on behalf of which the payment is effected (when applicable).<br>3. The amount paid.<br>4. Date of payment.<br>5. Type of application. | | | |
| Proof of Payment | | | |
| Summary of the protocol in English and/or Maltese | | | |
| Protocol with all current amendments | | | |
| Investigator's brochure | | | |
| Investigational Medicinal Product Dossier (IMPD) | | | |
| Simplified IMPD for known products | | | |
| Summary of Product Characteristics (for products with a marketing authorisation in the Community) | | | |
| List of Competent Authorities to which the application has been submitted and details of their decisions | | | |
| Copy of authorisation for contained use or release of genetically modified organisms (only applicable for GMO derived medicinal products) | | | |
| Informed consent form (in English **and** Maltese[1]) | | | |
| Subject information leaflet (in English **and** Maltese[1]) | | | |
| Outline of all active trials with the same IMP | | | |
| Copy of the manufacturer authorization referred to in Article 13(1) of Directive 2001/20/EC for IMPs manufactured in the EU/EEA and if no marketing authorisation in EU, or if the IMP is batch released in another EU/EEA country, the declaration of the qualified person for batch release is sufficient | | | |
| If IMP not manufactured in EU and no marketing authorisation in EU, | | | |

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|---|---|---|---|
| certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality | | | |
| Copy of the importer's manufacturing authorization as referred to in Article 13(1) of the Directive if IMP not manufactured in EU and no marketing authorisation in EU | | | |
| Copy of the wholesale distribution authorization (if product is sourced from EU wholesale dealers) | | | |
| Certificate of analysis for test product in exceptional cases: where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected | | | |
| Viral safety studies (for sterile agents and biological IMPs) | | | |
| IMP labels in English and/or Maltese | | | |
| TSE Certificate for IMPs derived from bovine materials | | | |
| Certification of GMP status of active biological substance if IMP not manufactured in EU and no marketing authorisation in EU | | | |
| CV of the coordinating investigator in the MS concerned for multicentre trials) | | | |
| CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator) | | | |
| Brief information about supporting staff (roles and responsibilities) | | | |
| Facilities for the trial | | | |
| Copy of the agreement between Sponsor/CRO and trial sites | | | |
| A letter from head of trial site stating his/her awareness of the clinical trial to be conducted at the site following an approval of the clinical trial by the Medicines Authority | | | |
| Informed consent letter of authorisation holder when cross-referencing is made. | | | |
| Proof of establishment of the sponsor or its legal representative in the community | | | |
| ➢ EudraCT number(s): | | N/A | N/A |
| ➢ Sponsor protocol number(s): | | N/A | N/A |
| Copy of the email containing the notification of the EudraCT number received by the applicant | | | |
| **Administrative details:** | | | |
| ➢ Details of any application submitted to the Medicines Authority for a trial involving the same active substance:<br><br>Previous application EudraCT numbers and Sponsor Protocol Number: | | | |

| | | | |
|---|---|---|---|
| Contact numbers and names (of the investigators and person responsible for pharmacovigilance) to be contacted in case of a crisis situation | | | |
| Declaration that all local investigators participating in the conduct of the trial should make themselves available and accessible to the Medicines Authority | | | |
| A letter of intent that the sponsor continues to supply the IMP to participants of the trial after the trial ends | | | |
| If the applicant is not the sponsor, they should enclose a letter from the sponsor authorising the applicant to act on their behalf | | | |

[1] **Documents given to patients should be translated in both English and Maltese. For documents to be submitted in Maltese, the sponsor may submit all documentation in English and submit a request so that the translated documents in Maltese can be submitted during the assessment of the Clinical Trial.**

Note that no approval will be granted to missing translated documents.

## 15 PAYMENT NOTIFICATION

Kindly note that whenever a payment is effected in respect of an application which is submitted to the Medicines Authority, the following details need to be submitted to Ms. Analisa Buttigieg on *analisa.buttigieg@gov.mt*:

1. The name of the company effecting payment
2. The name of the company on behalf of which the payment is effected (when applicable).
3. The amount paid.
4. Date of payment.
5. Type of application.

This information needs to be submitted on the date that the payment is effected.