

Information for applicants requesting the release of lots of clinical test material consisting of immunological medicinal products (starting document)

1 INTRODUCTION

In conformance with the Immunological Medicinal Products Decree, Article 5.1.e, certain unregistered immunological medicinal products (IMP) with which scientific medical research tests can be done on human subjects, can only be supplied if they are released in lots by the Chief Inspector of Pharmacy and Medical Technology from the Dutch Health Care Inspectorate.

2 DEFINITION

Lots released by the manufacturer after August 1, 2001 (the implementation date for the amended decree Immunological Medicinal Products) are subject to the release procedure for unregistered IMP's by the Chief Inspector of Pharmacy and Medical Technology. This also applies when lots that are used in a study that was started or approved by a Medical Ethical Committee before that date.

Lots released by the manufacturer before August 1, 2001 are not subject to the release procedure for unregistered IMP's by the Chief Inspector of Pharmacy and Medical Technology.

Unregistered IMP's, that must be released by the Chief Inspector for delivery for the purpose of scientific medical research on human subjects, are:

- a. Live vaccines
- b. IMP's that are used for the primary vaccination of infants or groups at risk.
- c. IMP's used in public health immunization programs.
- d. New IMP's or IMP's manufactured using new or altered kinds of technology or new for a particular manufacturer (for example, monoclonal antibodies for therapeutic and in vivo diagnostic application).

For certain new investigational medicines, it is not always clear if they fall within the definition of an IMP and thus are subject to the release procedure. A product is considered an IMP when its effect is based on an immunological interaction, i.e. antibody-antigen binding or a T-cell mediated immune response. In any case, the IMP's named below fall within the obligation of release by the Chief Inspector for Pharmacy and Medical Technology:

- All vaccines, including synthetic, autologous and plasmid DNA vaccines.
- Monoclonal antibodies, including fragments thereof and antibodies produced using recombinant DNA technology.
- Gene therapeutic substances, in case their mode of action is based on immunological principles.
- Toxins, in case their mode of action is based on immunological principles.
- Allergens produced using recombinant DNA technology.

Registered IMP's that are used for clinical studies to extend their indication or to justify major changes in the manufacturing process, may also be subject to the release procedure.

When the applicant is in doubt whether a specific product is subject to release in accordance to the amended decree, they can ask for an advice by sending an e-mail to the following address: bif-info@rivm.nl

3 CONFERRING WITH OTHER PARTIES

In accordance to current regulations, the protocol for the clinical study is also assessed by a Medical Ethical Committee (METC) or the Central Committee on Research Involving Human Subjects (CCMO). Subject to approval of the applicant, the secretariat for lot release may contact the organisation(s) involved to confer on their decision(s). This is done to prevent any overlap of the decisions of the METC and/or the CCMO and the release of lots by the Chief Inspector for Pharmacy and Medical Technology.

4 PROCEDURE

4.1 Secretariat for lot release

The Chief Inspector for Pharmacy and Medical Technology has charged the centre for Biological Medicines and Medical technology (BMT), previously known as Laboratory for Medicines and Medical Devices (LGM), of the National Institute for Public Health and the Environment (RIVM) with the administration and release of these lots of clinical test material. Thus, BMT is the contact address for the application for release of lots of unregistered IMP's.

4.2 Confidentiality

The release of a lot or lots of an unregistered IMP consists of an assessment of the documentation supplied by the applicant to ensure the quality and safety of the lot(s). All documents supplied are treated as strictly confidential. Any information related to an application for lot release, will only be given to the original applicant. Therefore, it is important to provide the secretariat with the correct name and address of applicant and contact person.

4.3 Payment

As determined in the Regulations of Release pursuant to Article 3a of the Medicines Act, the costs for processing an application for release is €4000,- (VAT-exempted). Proof of payment should be provided with the request for release. For payments by bank transfer:

Bank account 378 344 900
National Institute for Public Health and the Environment, Accounting Office
Swiftcode IBAN NL 36
Rabo International
PO Box 2626
3500 GP Utrecht
The Netherlands

Please state on the payment: "Lot release for Clinical Testing Material V/605900", name and number of the lot and the protocol number of the clinical study.

4.4 Application for lot release

An application for the release of a lot of an unregistered IMP should be directed to:

National Institute for Public Health and the Environment (RIVM)
Centre for Biological Medicines and Medical Technology
(Postage bag 50)
Attn. Lot Release for Clinical Testing Material
P.O. Box 1

3720 BA Bilthoven
The Netherlands

Telephone: +31 (0)30 274 2759
Fax: +31 30 274 4421/4422
e-mail: bif-info@rivm.nl

After BMT has received the request, the applicant will receive a written confirmation of receipt.

1. The request for release should be accompanied by (in triplicate):
 - A completed application form (see Annex 1). Please verify the most recent version is used.
 - Proof of payment of the costs.
 - A certificate of analysis for the lot concerned.

Chemical pharmaceutical documentation consisting of:

- * A completed supplementary questionnaire (see Annex 2). Please verify the most recent version is used.
- * Quantitative and qualitative composition of the IMP.
- * Description of product development, including development genetics, cell line used for production, cell banking system, as appropriate.
- * Description of the production process, including cell culture conditions, harvesting procedure or synthesis procedures, down-stream processing, purification process, in-process controls, control of critical steps and intermediates, process validation or evaluation and virus testing, as appropriate.
- * Control of raw materials, starting materials, active ingredients and end product, including specifications, analytical procedures, reference and control materials, product characterisation or structural analysis and impurities, as appropriate.
- * Data regarding the microbial quality and viral safety of the product and any biological components it contains
- * Data about the shelf life and storage conditions of the product and the lot concerned.
- * Test results of in-process controls and on end product for the lot concerned (certificate of analysis, release certificate of manufacturer).

Pre-clinical and clinical documentation consisting of:

- * A description of the predicted efficacy of the IMP insofar as it is known, a statement of the intended indications, the contra-indications side effects, as well as a statement of the dosage, the way it is to be used and the means of administration of the IMP, as appropriate.
- * Data of clinical nature, e.g. results of any previous clinical studies.
- * A statement of all the results of the pharmacological and toxicological studies of the IMP and of the active ingredients of the IMP.
- * The protocol of the clinical study concerned.
- * The most recent version of the Investigator's Brochure for the clinical study for which the lot is used.

The data provided must be either in Dutch or in English.

See also: Supplementary list of questions for the release of lots of unregistered immunological questions for clinical studies (Annex 2).

At this time, there are no demands on the format for the documentation. When possible, the data should be presented in the format of the Common Technical Document (The Rules Governing Medicinal Products in the European Union, Volume 2, Notice to Applicants, Volume 2B, Presentation and Content of the Dossier, Common Technical Document (adopted July 2001); <http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctdmay02.pdf>).

The documentation should be concise and data preferably presented in a tabular form, but most importantly, the documentation should be clear, straightforward and accessible.

4.5 Assessment of data provided

The dossier will be assessed by BMT, who will inform the Chief Inspector for Pharmacy and Medical Technology of their judgement. The final decision is made by the Chief Inspector for Pharmacy and Medical Technology, who will give written notice about the release of a lot of an unregistered IMP to the applicant. The applicant is notified within a period of 60 days after submission of the application for release. The period of 60 days begins as soon as all the necessary documentation and proof of payment is received.

When the submitted documentation gives cause, the secretariat can ask the applicant for additional information. The clock for the 60-day period stops as soon as a request for additional information is made. As soon as the requested information is received, the clock starts again.

When the application for release concerns a product that is registered as a medicine in a member state of the EU and the lot has been released by an official government authority of that member state, then the release of this lot is recognised. In that case, a copy of the release certificate must be produced and the applicant is exempted from paying the fee.

When the application for release concerns a number of lots for **the same clinical study**, a complete request for the release of each separate lot must be submitted. However, the fee is paid only once.

When for **the same clinical study**, the release for an additional new lot is requested, a complete application for the release of that lot must be submitted, including full payment of the fee.

After a negative decision by the Chief Inspector for Pharmacy and Medical Technology for release, a new application for that lot may be submitted when the applicant can provide sufficient new data. The release procedure is started again, including supplying all documentation and full payment of the fee.

When the study protocol is changed after the lot has been released, the applicant should request a revision of the release in case it involves a change in the intended indication, contra-indication, dosage, usage or administration.

Also in case the lot is to be used in a different clinical study.

When the amended or new study protocol necessitates a new assessment, a new application for lot release should be filed, including full payment of the fee. The applicant is notified after the relevant documentation has been supplied for review.

- Annex 1:* Application form for the release of unregistered immunological pharmaceutical products
- Annex 2:* Supplementary list of questions for the release of lots of unregistered immunological questions for clinical studies (chemical-pharmaceutical documentation).