Agence Fédérale des Médicaments
et des Produits de Santé

VOTRE LETTRE DU
VOS REF.
NOS REF. AFMPS/O&O/KFB/96852
DATE
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Circulaire n° 567

A l'attention des promoteurs

A l'attention des fabricants de médicaments expérimentaux

A l'attention des pharmaciens d'hôpitaux

A l'attention des médecins-chefs d'hôpitaux

A l'attention des directeurs d'hôpitaux

OBJET **Activités de production des médicaments expérimentaux**

Madame, Monsieur,

1. Exigences légales en matière de production des médicaments expérimentaux

La nécessité d'une autorisation pour la fabrication des médicaments expérimentaux (Investigational Medicinal Products ou IMPs) est décrite à l'article 24 de la loi du 07/05/2004 relative aux expérimentations sur la personne humaine:

Art. 24. § 1er. Pour la fabrication et l'importation de médicaments expérimentaux, une autorisation accordée par le ministre est requise. Une autorisation est aussi requise si le médicament expérimental est fabriqué en vue d'être exporté.

L'AR du 30/06/2004 décrit cela de façon détaillée:

Art. 16. § 1er. L'autorisation prévue à l'article 24, § 1er, de la loi du 7 mai 2004 susmentionnée est exigée tant pour la fabrication totale ou partielle de médicaments expérimentaux que pour des opérations de division et de conditionnement. Cette autorisation est requise même si les produits fabriqués sont destinés à être exportés.

Une autorisation d'importation est requise pour les importations provenant de pays tiers.

§ 2. L'autorisation prévue à l'article 24, § 1er de la loi du 7 mai 2004 susmentionnée n'est toutefois pas requise pour la reconstitution préalable à l'utilisation ou le conditionnement lorsque ces opérations sont effectuées dans des hôpitaux, des centres de santé ou des cliniques, par les pharmaciens et si les médicaments expérimentaux sont destinés à être utilisés exclusivement dans ces institutions.

Les services concernés de l'Agence Fédérale des Médicaments et des Produits de Santé (AFMPS) sont toutefois conscients du manque de clarté relatif au domaine d'application de ces dispositions. C'est pourquoi l'AFMPS a rédigé la présente circulaire dans laquelle les différentes possibilités sont décrites. Le rôle des différents intéressés y est également expliqué en détail. Suite à la parution de la circulaire, nous demandons aux intéressés de se manifester et de se mettre en règle si cela n'a pas encore été fait.

2. Possibilités

2.1 Titulaires d'autorisation selon l'AR du 30/06/2004

Une autorisation 30/06/2004 est nécessaire pour fabriquer un médicament expérimental à partir de ses composants. Une telle autorisation ne sera accordée que si le fabricant répond aux conditions, ce qui sera vérifié par une inspection. Chaque instance peut introduire une demande pour une autorisation de ce type, qu'il s'agisse d'une société pharmaceutique, d'un centre de phase I, d'une pharmacie hospitalière ou d'une autre "instance".

2.2 Pharmacie hospitalière

Comme indiqué dans l'AR du 30/06/2004, la pharmacie hospitalière peut être responsable de la reconstitution ou du conditionnement à condition que le médicament expérimental soit utilisé dans l'établissement auquel la pharmacie hospitalière est attachée.

La reconstitution est considérée comme le processus lors duquel :

- le médicament expérimental est dissout ou dispersé avant d'être administré à un des participants de l'étude

OU

- le médicament expérimental est dilué ou mélangé avec d'autres substances destinées à servir de véhicule à des fins d'administration.

Ce processus doit être décrit dans la demande d'essai clinique (Clinical Trial Application- CTA) et dans un document disponible sur le site où l'étude sera effectuée. L'administration doit se faire le plus vite possible après la reconstitution.

Le mélange de différents ingrédients, substance active comprise, pour produire l'IMP NE peut être considéré comme une reconstitution. Un IMP doit être libéré par une personne qualifiée européenne (EU Qualified Person – QP) avant qu'un processus puisse être considéré comme une reconstitution.

Si une pharmacie hospitalière veut effectuer des opérations supplémentaires, une demande d'autorisation conforme à l'AR 30/06/2004 doit être introduite (voir point 2.1), ou une inspection doit être demandée dans le cadre du projet "minimal GMP requirements for phase I trials" (voir plus loin).

2.3 Centres de phase I

Vu que les centres d'étude de phase I ne sont pas définis dans la législation belge, il n'est pas toujours évident pour un tel centre de savoir quelle est au juste la réglementation. Pour un centre de phase I, il y a également deux possibilités : soit une demande d'autorisation conforme à l'AR 30/06/2004 est introduite (voir point 2.1), soit une inspection est demandée dans le cadre du projet "minimal GMP requirements for phase I trials" (voir plus loin).

3. Procédures

L'AFMPS autorise une période de transition durant laquelle les différents intéressés sont invités à se manifester et à faire un choix clair entre les deux procédures ci-dessous. Cette période transitoire prendra fin le 15/06/2010. Les demandes d'essais cliniques auxquels participent des instances qui ne se sont pas mises en règle seront immédiatement refusées après cette date.

Toutes les demandes seront examinées dans le courant de l'année 2010 et début 2011, toutes les procédures seront en principe terminées.

3.1 Inspection sur base du document "GMP requirements for early phase trials"

Une telle inspection examinera uniquement si les différents aspects qui sont listés dans le document *"GMP requirements for early phase trials"* (voir document en annexe 2)
sont présents. Des activités de production limitées et décrites clairement sont possibles, en concertation avec l'/les inspecteur(s) concerné(s).

Il faut clairement insister sur le fait que les activités du demandeur d'une "early phase inspection" se limitent à la reconstitution / au conditionnement / à la production (si d'application) pour:

- o des études dans la phase exploratoire ou phase I / II qui tombent sous la définition d'études "early phase". (pour la définition, voir annexe 1)

ET

- o l'utilisation dans le centre / l'instance / concerné(e)... (donc pas pour une distribution ultérieure hors du centre ou de l'instance).

En outre, AUCUNE autorisation n'est délivrée à la suite d'une inspection de ce type – le rapport et les conclusions éventuelles sont cependant bien utilisés pour vérifier des futures demandes d'essais cliniques – cela signifie que des futures demandes d'essais cliniques seront refusées si des opérations sont nécessaires pour ces essais et ne peuvent être effectuées correctement selon les résultats de l'inspection.

"Early phase GMP" est un projet au sein de l'AFMPS. Les résultats de ce projet démontreront si une approche spécifique pour les études "early phase" est nécessaire ou non.

3.2 Demande AR 30/06/2004

La demande d'autorisation – AR 30/06/2004 (nouvelle demande, demande de modification de l'autorisation ou demande de modification des installations reconnues) doit être introduite avec tous les documents exigés auprès de l'Agence Fédérale des Médicaments et des Produits de Santé, Eurostation, Bloc II, 8e étage, Place Victor Horta 40, boîte 40 à 1060 Bruxelles.

Plus d'informations sur :

http://www.fagg-afmps.be/fr/humain/medicaments/medicaments/autorisations/autorisation_ar-30-06-04/index.jsp

Cette autorisation est l'"autorisation standard" qui est également accordée aux firmes pharmaceutiques. L'instance qui les demande doit respecter les principes et les lignes directrices en matière de bonnes pratiques pour la fabrication de médicaments expérimentaux. Les dispositions telles que décrites dans l'AR du 30/06/2004 s'appliquent.

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4. **Demande d'autorisation ou d'inspection**

Comme indiqué ci-dessus, il est attendu de chaque instance qui effectue les opérations susmentionnées qu'elle se manifeste avant le 15/06/2010. Les différentes possibilités sont :

- pour la pharmacie hospitalière :
    - uniquement reconstitution / conditionnement tel que décrit(e) dans l'AR du 30/06/2004 → pas d'autre action exigée ;
    - production limitée dans le cadre d'études early phase pour utilisation dans l'établissement → formulaire en annexe 3, choix "early phase" ;
    - production → formulaire en annexe 3, choix "autorisation 30/06/2004".
- pour d'autres instances (centre de phase I, producteurs de radiopharmaceutiques dans les hôpitaux, ...) :
    - reconstitution / conditionnement / production dans le cadre d'études early phase pour utilisation dans l'établissement → formulaire en annexe 3, choix "early phase" ;
    - production → formulaire en annexe 3, choix "autorisation 30/06/2004".

Nous vous remercions de l'attention que vous accorderez à cette circulaire.

Veuillez agréer, Madame, Monsieur, l'assurance de notre considération distinguée,

Xavier De Cuyper
Adminstrateur-général

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ANNEXE 1 : définition d'une étude "early phase"

In this circular letter, should be considered to be early-phase trials:

- exploratory clinical trials (microdose – phase 0)
- phase I trials
- phase II trials :
    - first exposure to patients
    - exploring therapeutic effect / maximum tolerated dose
    - therapeutic dose finding in patients
- the first administration to children (especially neonates and toddlers)

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ANNEXE 2: GMP requirements for early phase trials

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GMP requirements for early phase trials

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INTRODUCTION

There is still need for guidance on the implementation of GMP in early phase clinical trials. This document is a working document that will be evaluated. The experiences in practice will then be used to refine the document.

SCOPE

Minimum GMP requirements for the preparation of medicinal products in inspected locations and to be used in early phase clinical trials at the same institution.

GLOSSARY

Blinding
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.

Clinical trial
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational 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.

Comparator product
An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Inspected location
A dedicated area, or an area providing equivalent protection, of the hospital pharmacy or the phase I unit inspected by the National Competent Authority

for the preparation of investigational medicinal products under minimum GMP conditions described in this document, intended for use on site.

Dispensing
The process of transferring a released investigational medicinal product from its primary packaging into a dispenser. Examples of a dispenser include a syringe, a bottle or a cup. Dispensing could be done up to 24 hours prior to administration, otherwise it should be considered as primary packaging. Reconstitution can be seen as part of the dispensing process.

Internal transfer
The operation of packaging for internal transfer of ordered investigational medicinal products for clinical trials to the investigator. Transfer processes may reflect the hospital's own processes or be tailored to meet the protocol's needs.

Investigational medicinal product
A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when 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.

Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Manufacturer/importer of Investigational Medicinal Products
Any holder of the authorisation to manufacture/import referred to in Article 13.1 of Directive 2001/20/EC.

Order
Instruction to process, package and/or transfer internally a certain number of units of investigational medicinal product(s).

Preparation
All processes and operations with an investigational medicinal product or placebo, from starting material until its completion, performed in a hospital pharmacy or phase I unit.

Primary packaging
The container or other form of packaging immediately in contact with the medicinal or investigational medicinal product.

Product Specification File
A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

Quality Agreement
A written agreement between the Qualified Person of the sponsor and the Responsible Person describing procedures and responsibilities of each party, and in accordance with applicable legislation.

Randomisation
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation Code
A listing in which the treatment assigned to each subject from the randomisation process is identified.

Reconstitution
Reconstitution is a simple process of:

- dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject,
- or, diluting or mixing the investigational medicinal product(s) with some other substance(s) used as a vehicle for the purposes of administering it,
- and, this process is defined in the Clinical Trial Application/IMP Dossier

  and clinical trial protocol, or related document, available at the site,
- and, this process is undertaken as soon as practicable before administration.

A released investigational medicinal product must exist before a process can be defined as reconstitution.

Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product

Responsible Person
An individual who takes responsibility for pharmaceutical operations performed in the inspected location. This should be a health care professional legally authorised to perform these activities.

Secondary packaging
The packaging into which the primary container is placed.

Sponsor
An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

QUALITY MANAGEMENT

1. The quality system, designed, set up and verified by the responsible person, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products. For each trial, a quality agreement between the qualified person of the sponsor and the responsible person should be in place.

2. The product specifications and preparation instructions may be changed during development but full control and traceability of the changes should be maintained.

PERSONNEL

3. All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.

4. The responsible person should in particular be responsible for ensuring that there are systems in place that meet the requirements of this document and should therefore have knowledge of pharmaceutical development and clinical trial processes. Separate people should be responsible for preparation and release. Both should have the knowledge necessary to perform this kind of operation.

PREMISES AND EQUIPMENT

5. The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection / test methods and acceptance limits to be used after cleaning should reflect the nature of these risks. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

DOCUMENTATION

Specifications and instructions

6. Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), preparation formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, and should allow traceability to the previous document. Any changes should be carried out according to a written procedure, which should address any implications for product quality such as stability and bio equivalence. The responsibility of the sponsor at this stage should be described in the written agreement

7. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and documented.

Order

8. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised, referring to the Product Specification File and the relevant clinical trial protocol and should be kept in the trial file at the inspected location.

Product Specification File

9. The Product Specification File (see glossary) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions and available for the responsible person if relevant.

Preparation Formulae and Processing Instructions

10. For every preparation operation or supply there should be clear and

    adequate written instructions and written records.

11. The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.

Packaging Instructions

12. If possible, investigational medicinal products are packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

Processing, testing and packaging batch records

13. Preparation records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify the procedures used and any changes made, should enhance knowledge of the product and should help developing the preparation operations.

14. Preparation records should be retained at least for the periods specified in Directive 2003/94/EC.

PREPARATION

Packaging materials

15. Specifications and quality control checks should include measures to guard against unintentional unblinding due to differences in appearance between different batches of packaging materials.

Preparation operations

16. During development evolution in parameters and process should be communicated by the sponsor to the responsible person.

17. Preparation processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to ensure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.

18. Validation of aseptic processes presents special problems when the batch size is small; in these cases the number of units filled may be the maximum number filled in production. If feasible, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility so enhanced attention should be given to operator training, and validating the aseptic technique of individual operators.

Principles applicable to comparator product

19. If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.

20. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable expiry date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility between the expiry date and the clinical trial duration.

Blinding operations

21. Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products when necessary, including the batch numbers of the products before the blinding operation. Rapid product identification should also be possible in case of emergency.

Randomisation code

22. Procedures should describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.

Packaging

23. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product mix up must be minimised by using appropriate procedures and/or, specialised equipment as well as appropriate and relevant staff training.

24. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than for marketed products, particularly when "blinded" products with similar appearance are used. Precautions against mislabelling such as label reconciliation, line clearance, in process control checks by appropriately trained staff should accordingly be double-checked.

25. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

Labelling

26. Labelling should comply with the requirements of Directive 2003/94/EC. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:

    a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);
    b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;
    c) the batch and/or code number to identify the contents and packaging operation;
    d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

e) the trial subject identification number/treatment number and where relevant, the visit number;
f) the name of the investigator (if not included in (a) or (d));
g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
h) "For clinical trial use only" or similar wording;
i) the storage conditions;
j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.
k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subjects have been given a leaflet or card providing these details and have been instructed to keep this in their possession at all times.

28. Particulars should appear in the 3 official languages. The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30). Other languages may be included. On condition that the trial medication is administered by trial personnel and is not taken home by the trial subjects, it is acceptable however that the label of the study medication is available in only one official language or in English language.

29. When the product is to be provided to the trial subject or the person administering the medication within a primary package together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in paragraph 26, the following information shall be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):

a) name of sponsor, contract research organisation or investigator;
b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number.

30. If the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in paragraph 26 cannot be displayed, secondary packaging should be provided bearing a label with those particulars. The primary packaging should nevertheless contain the following:

a) name of sponsor, contract research organisation or investigator;

b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number;

31. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

32. For clinical trials with the characteristics identified in Article 14 of Directive 2001/20/EC, the following particulars should be added to the original container but should not obscure the original labelling:
    i) name of sponsor, contract research organisation or investigator;
    ii) trial reference code allowing identification of the trial site, investigator and trial subject.

33. If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational medicinal product by order of the sponsor. This additional label should state the new expiry date and repeat the batch number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original batch number. It should be performed at the investigational site by or under the supervision of the responsible person. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and should be checked by a second person. This additional labelling should be properly documented as described in the quality agreement.

QUALITY CONTROL

34. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each preparation batch meets its specification.

35. Quality control should be performed in accordance with the Product Specification File and in accordance with the information notified pursuant to Article 9(2) of Directive 2001/20/EC. Verification of the effectiveness of blinding should be performed and recorded.

36. Samples of the investigational medicinal product should be retained to fulfil two purposes: firstly to provide a sample for analytical testing and secondly to provide a specimen of the finished product. Samples may therefore fall into two categories:

    Reference sample: a sample of a batch of starting material, packaging material, product contained in its primary packaging or finished product which is stored for the purpose of being analysed should the need arise.

    Retention sample: a sample of a packaged unit from a batch of finished product for each packaging run/trial period. It is stored for identification purposes. For example, presentation, packaging, labelling, leaflet, batch number, expiry date should the need arise.

In many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable. Reference and retention samples of investigational medicinal products, including blinded product, should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

Consideration should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as a part of an investigation into inconsistent trial results.

Note: Reference/retention samples are not applicable for dispensing and/or reconstitution operations, since it concerns already released investigational medicinal products.

37. All responsibilities regarding the number and storage of reference and retention samples should be defined in the Quality Agreement between the responsible person and the qualified person of the sponsor.

    The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the IMP Dossier submitted for authorisation to conduct the clinical trial. The number of retention samples could, however, be limited upon documented justification.

    In the case of retention samples, it is acceptable to store information related to the final packaging as written or electronic records if such records provide sufficient information.

RELEASE OF BATCHES

38. Release of investigational medicinal products (see paragraph 41) should not occur until after the responsible person has certified that the requirements of the present document have been met. The responsible person should take into account the elements listed in paragraph 39 as appropriate.

39. The responsible person may only release products prepared in the concerned inspected location and intended to be used on site. [If they are not used on site, GMP (Eudralex volume 4) applies.] Assessment of each batch for certification prior to release may include as appropriate:
    a) batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, the protocol and the randomisation code. These records should include all deviations or planned changes and any consequent additional checks or tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
    b) production conditions;
    c) the validation status of facilities, processes and methods;

d) examination of finished packs;
e) where relevant, the results of any analyses or tests performed after importation;
f) stability reports;
g) the source and verification of conditions of storage and shipment;
h) audit reports concerning the quality system of the inspected location;
i) verification that all raw materials supplied by the sponsor have been adequately released by the qualified person (e.g. by means of a QP statement from the sponsor);
j) certificates of analysis for commercially available starting materials not supplied by the sponsor
k) all other factors of which the responsible pharmacist is aware that are relevant to the quality of the batch;
l) documents certifying that the location is inspected by the National Competent Authority to prepare investigational medicinal products or comparators

The sponsor should ensure that the elements taken into account by the qualified person when certifying the batch are consistent with the information notified pursuant to Article 9(2) of Directive 2001/20/EC.

See also 45.

DISPENSING

40. A written dispensing procedure should be approved by the qualified person and dispensing operations should be double-checked by a second person.

41. Investigational medicinal products should not be dispensed until released by the responsible person.

42. Simplified labelling of the dispenser could be applied, but the label should nevertheless contain at least the following information:

a) route of administration (may be omitted for oral solid dosage forms);
b) the trial subject information number/treatment number and where relevant, the visit number

INTERNAL TRANSFER

43. A transfer procedure should be written according to the instructions given by the sponsor. A transfer document has to be signed for traceability and formalisation of taking charge of the product(s).

44. Investigational medicinal products should not be transferred to the investigator until released by the responsible person.

45. All investigational medicinal products should be traceable from the inspected location to the trial subject.

46. It is not allowed to transfer Investigational Medicinal Products from the inspected location to another trial site.

COMPLAINTS

47. The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed

    between the responsible person and the sponsor. This should involve the qualified person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

RECALLS AND RETURNS

Recalls

48. A procedure has to be approved by the sponsor and followed by the responsible person.

49. The sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the sponsor the need to recall any product supplied.

Returns

50. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.

51. Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

DESTRUCTION

52. The sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written confirmation of the sponsor.

53. The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and

satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the sponsor.

54. When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

Agence Fédérale des Médicaments et des
Produits de Santé

ANNEXE 3 de la circulaire 567: FORMULAIRE DE NOTIFICATION

Dénomination complète:	
Adresse: Siège social Numéro d'entreprise	
Nom et prénom du/des demandeur(s) Responsable, autorisé par les statuts à signer cette demande	
Type de demandeur: Pharmacie hospitalière Centre Phase 1 Autre instance	☐ ☐ ☐
Personne de contact Nom: Adresse: téléphone e-mail	
Procédure: Aucune – uniquement reconstitution/ conditionnement (seulement pour les pharmacies hospitalières) Inspection dans le cadre de l'"early phase GMP" Demande selon l'AR 30/06/2004 (ajouter autres documents!)	☐ ☐ ☐

Envoyer à : ct.rd@fagg.be (version électronique)
Ou à l'adresse ci-dessous à l'attention de "Division Recherche et Développement"

Agence Fédérale des Médicaments et des Produits de Santé
Eurostation II
Place Victor Horta 40/40
1060 Bruxelles