Federaal Agentschap voor Geneesmiddelen
en Gezondheidsproducten

UW BRIEF VAN
UW REF.
ONZE REF. FAGG/O&O/KFB/96852
DATUM
BIJLAGE(N) /
CONTACT
TEL. 02 524 80 00
FAX 02 524 80 01
E-MAIL ct.rd@fagg-afmps.be

Omzendbrief nr. 567

Aan opdrachtgevers van klinische proeven
Aan producenten van geneesmiddelen voor onderzoek

Aan de ziekenhuisapothekers

Aan de hoofdgeneesheren van de ziekenhuizen

Aan de ziekenhuisdirecties

BETREFT **Productie-activiteiten met geneesmiddelen voor onderzoek**

Geachte Mevrouw, Geachte Heer,

1. Wettelijke vereisten voor het produceren van geneesmiddelen voor onderzoek

De wet inzake experimenten op de menselijke persoon dd. 07/05/2004 beschrijft in artikel 24 de noodzaak voor een vergunning voor de vervaardiging van geneesmiddelen voor onderzoek (Investigational Medicinal Products of IMPs):

Art. 24. § 1 Voor de vervaardiging en de invoer van geneesmiddelen voor onderzoek is een vergunning vereist, verleend door de minister. Een vergunning is ook vereist indien het geneesmiddel voor onderzoek wordt vervaardigd met het oog op uitvoer.

Het KB van 30/06/2004 beschrijft dit verder:

Art. 16. § 1. De in artikel 24, § 1, van bovenvermelde wet van 7 mei 2004 bedoelde vergunning is voor zowel volledige als gedeeltelijke vervaardiging van geneesmiddelen voor onderzoek vereist, alsmede voor de diverse procédés voor het opsplitsen en verpakken. De vergunning is ook vereist indien de vervaardigde producten voor de uitvoer zijn bestemd.

Een vergunning voor invoer is vereist voor de invoer uit derde landen.

§ 2. De in artikel 24, § 1, van bovenvermelde wet van 7 mei 2004 bedoelde vergunning is evenwel niet vereist voor de aan het gebruik voorafgaande reconstitutie of voor het verpakken indien deze verrichtingen in ziekenhuizen, gezondheidscentra of klinieken worden uitgevoerd door apothekers en indien de geneesmiddelen voor onderzoek uitsluitend voor gebruik in die instellingen bestemd zijn.

De betrokken diensten van het Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) realiseren zich echter dat er nog steeds onduidelijkheden bestaan rond het toepassingsgebied van deze bepalingen. Daarom werd door het FAGG een document opgesteld waarin de verschillende mogelijkheden worden beschreven. De rol van de verschillende belanghebbenden wordt in deze omzendbrief verder uitgeklaard. Aan de belanghebbenden wordt gevraagd zich kenbaar te maken en zich in regel te stellen indien dit nog niet zou gebeurd zijn.

2. Mogelijkheden

2.1 Vergunningshouders volgens het KB van 30/06/2004

Om een geneesmiddel voor onderzoek te vervaardigen vanuit zijn bestanddelen, is een vergunning 30/06/2004 noodzakelijk. Alvorens een dergelijke vergunning zal worden toegekend, zal door middel van een inspectie worden nagegaan of aan de voorwaarden wordt voldaan. Elke instantie kan een dergelijke vergunning aanvragen, ongeacht of ze een farmaceutische firma, een fase I centrum, een ziekenhuisapotheek of een andere "instantie" is.

2.2 Ziekenhuisapotheek

Zoals vermeld in het KB van 30/06/2004 kan de ziekenhuisapotheek instaan voor de reconstitutie of voor het verpakken mits het geneesmiddel voor onderzoek wordt gebruikt binnen de instelling waarvoor de ziekenhuisapotheek instaat.

Reconstitutie wordt beschouwd als het proces waarbij:

- het geneesmiddel voor onderzoek wordt opgelost of gedispergeerd alvorens toediening aan een proefpersoon

OF

- het geneesmiddel voor onderzoek wordt verdund of gemengd met andere substanties bedoeld als vehiculum voor toedieningsdoeleinden.

Dit proces moet beschreven zijn in de aanvraag voor klinische proef, het geneesmiddeldossier (Investigational Medicinal Product Dossier - IMPD), het protocol of een ander document beschikbaar op de site waar de proef zal worden uitgevoerd. De toediening moet zo snel mogelijk na de reconstitutie gebeuren.

Het mengen van verschillende ingrediënten, de actieve substantie inbegrepen, om het IMP te produceren kan NIET beschouwd worden als reconstitutie. Een IMP moet vrijgegeven zijn door een Europese bevoegde persoon (EU Qualified Person – QP) alvorens een proces kan beschouwd worden als reconstitutie.

Indien een ziekenhuisapotheek bijkomende handelingen zou willen uitvoeren, moet een vergunning volgens het KB 30/06/2004 worden aangevraagd (zie punt 2.1), of moet een inspectie worden aangevraagd in het kader van het project "minimal GMP requirements for phase I trials" (zie verder).

2.3 Fase I – centra

Gezien fase I-onderzoekscentra niet gedefinieerd zijn in de Belgische wetgeving, is het voor een dergelijk centrum niet altijd duidelijk wat nu juist de regelgeving is. Voor een fase I- centrum zijn er eveneens twee mogelijkheden: ofwel wordt een vergunning volgens het KB 30/06/2004 aangevraagd (zie punt 2.1), of wordt een inspectie aangevraagd in het kader van het project "minimal GMP requirements for phase I trials" (zie verder).

3. Procedures

Het FAGG laat een overgangsperiode toe waarin verwacht wordt van de verschillende betrokkenen dat ze zich kenbaar maken, en dat ze een duidelijke keuze maken tussen de twee onderstaande procedures. Deze overgangsperiode zal lopen tot 15/06/2010. Aanvragen voor klinische proeven waaraan instanties deelnemen die zich niet in regel gesteld hebben, zullen na deze datum onmiddellijk geweigerd worden.

Verwacht wordt dat in de loop van 2010 alle aanvragers bezocht zullen worden en dat tegen begin 2011 alle procedures doorlopen zullen zijn.

F
AFMPS
A
G

3.1 Inspectie op basis van het document "GMP requirements for early phase trials"

Een dergelijke inspectie zal louter nakijken of de verschillende aspecten die in het document "GMP requirements for early phase trials" (zie document in bijlage 2) worden opgelijst, aanwezig zijn. Beperkte en duidelijk beschreven productie-activiteiten zijn mogelijk, in overleg met de betrokken inspecteur(s).

Er moet duidelijk benadrukt worden dat de activiteiten van de aanvrager van een "early phase inspectie" zich beperken tot reconstitutie / verpakking / productie (indien van toepassing) voor:

- o proeven in de exploratieve fase of fase I / II die binnen de definitie van early phase proeven vallen. (voor de definitie zie bijlage 1)

EN

- o gebruik binnen het betrokken centrum / instantie / ... (dus niet voor verdere distributie buiten het centrum of de instantie).

Tevens wordt GEEN vergunning uitgereikt naar aanleiding van een dergelijke inspectie – het rapport en de eventuele conclusies worden echter wel gebruikt ter verificatie van toekomstige aanvragen voor klinische proeven – dit wil zeggen dat bij negatieve bevindingen toekomstige aanvragen voor klinische studies geweigerd zullen worden indien voor deze studie handelingen nodig zijn die volgens deze bevindingen niet correct kunnen worden uitgevoerd.

"Early phase GMP" is een project binnen het FAGG. De resultaten van dit project zullen uitwijzen of een specifieke approach voor early phase proeven al dan niet noodzakelijk is.

3.2 Aanvraag KB 30/06/2004

De vergunningsaanvraag – KB 30/06/2004 (nieuwe aanvraag, aanvraag tot wijziging van de vergunning of aanvraag tot wijziging van de erkende installaties) moet ingediend worden met alle vereiste documenten bij het Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten, Eurostation, Blok II, 8e verdieping, Victor Hortaplein 40, bus 40 te 1060 Brussel.

Meer informatie op :

http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/vergunningen/vergunning_KB_30_06_2004/

Deze vergunning is de "standaardvergunning" die ook aan farmaceutische firma's kan worden toegekend. De instantie die ze aanvraagt, moet de beginselen en richtsnoeren inzake goede praktijken bij het vervaardigen van geneesmiddelen voor onderzoek naleven. De bepalingen zoals beschreven in het KB van 30/06/2004, gelden.

F
AFMPS
G
G

4. Aanvraag voor vergunning of inspectie

Zoals hierboven vermeld, wordt van elke instantie die bovenvermelde handelingen uitvoert, verwacht dat ze zich kenbaar maakt voor 15/06/2010. De verschillende mogelijkheden zijn :

- voor de ziekenhuisapotheek :
    - enkel reconstitutie / verpakking zoals beschreven in het KB van 30/06/2004 → formulier in bijlage 3, keuze "enkel reconstitutie / verpakking"
    - beperkte productie in het kader van early phase proeven voor gebruik binnen de instelling → formulier in bijlage 3, "early phase";
    - productie → formulier in bijlage 3, "vergunning 30/06/2004".
- voor andere instanties (fase I centra, producenten van radiofarmaca in ziekenhuizen, ...):
    - reconstitutie / verpakking / productie in het kader van early phase proeven voor gebruik binnen de instelling → formulier in bijlage 3, "early phase";
    - productie → formulier in bijlage 3, "vergunning 30/06/2004".

Wij danken u voor de aandacht die u aan deze omzendbrief zal besteden en verblijven inmiddels met de meeste hoogachting,

Xavier De Cuyper
Administrateur-Generaal

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
Eurostation II
Victor Hortaplein 40/40
1060 Brussel
.be

F
AFMPS
G
G

BIJLAGE 1 : definitie early-phase studie

In this circular letter, one should consider 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)

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
Eurostation II
Victor Hortaplein 40/40
1060 Brussel

F
AFMPS
G
G

BIJLAGE 2 : GMP requirements for early phase trials

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
Eurostation II
Victor Hortaplein 40/40
1060 Brussel

.be

GMP requirements for early phase trials

Federal Agency for Medicines and Health Products
Eurostation II
Place Victor Horta 40/40
1060 Brussels
0884.579.424
www.afmps.be

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.

F
AFMPS
G

BIJLAGE 3 AAN OMZENDBRIEF 567 : AANMELDFORMULIER

Volledige benaming :	
Adres : Maatschappelijke zetel Ondernemingsnummer	
Naam en voornaam van de aanvrager(s) Verantwoordelijke, door de statuten gemachtigd deze aanvraag te tekenen	
Type aanvrager : Ziekenhuisapotheek Fase 1 - centrum Andere instantie	☐ ☐ ☐
Contactpersoon Naam : Adres : telefoon e-mail	
Procedure : Geen – enkel reconstitutie / herverpakking (enkel voor ziekenhuisapotheken) Inspectie in het kader van "early phase GMP" Aanvraag volgens KB 30/06/2004 (verdere documentatie bezorgen !)	☐ ☐ ☐

Terug te sturen aan : ct.rd@fagg.be (elektronische versie)
of onderstaand adres t.a.v. "Afdeling Onderzoek & Ontwikkeling"

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
Eurostation II
Victor Hortaplein 40/40
1060 Brussel
.be