Clinical Trials Facilitation Groups

Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications

Version 2

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1 Abbreviations

CA	competent authority
CT	clinical trial
CTFG	clinical trial facilitation group
CTA	clinical trial application
EC	ethics committee
EU	European Union
FIH	first in human
HMA	EU Heads of Medicines Agencies
MN-FIH	multinational first in human
GNA	grounds for non acceptance
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
MA	marketing authorisation
MC-CT	multicentre clinical trial
MS	member state
MN-CT	multinational clinical trial
NIMP	Non IMP
NCA	national competent authority
P-NCA	participating national competent authority
PIP	paediatric investigational Plan
RFI	request for further information
VHP	voluntary harmonisation procedure
VHP-C	VHP-Coordinator
VHP-SA	substantial amendment of a positive Voluntary Harmonisation Procedure

2 Introduction

The EU Heads of Medicines Agencies (HMA) agreed in 2004 to establish a clinical trials facilitation group (CTFG) to co-ordinate the implementation of the EU clinical trials directive 2001/20 EC across the member states
This document is produced by the CTFG in order to propose a harmonised procedure for assessing multinational clinical trials (CT) by the National Competent Authorities (NCA) in EU. The changes of this new version of the guideline were approved by the HMAs during the November 2009 Meeting in Uppsala; Sweden.
This document should be read in conjunction with other EU-published guidelines (see also Section References).

The main changes in v2 with respect to v1 refer to:
a) the acceptability of all CTs with at least 3 concerned MS;
b) deletion of the *"Pre-procedural step" or "Request for VHP"* phase in the procedure, and
c) the inclusion of substantial amendments in the scope of the VHP.

The CTFG is open for discussions on further improvements especially in respect of handling substantial amendments. Any suggestion in this respect should be sent to VHP-CTFG@VHP-CTFG.eu indicating on the message reference "suggestion for improvement of VHP".

3 Background/Rationale

The Directive 2001/20/EC, (the "EU Clinical Trials Directive"), relating to the implementation of good clinical practice in the conduct of clinical trials (CT) on medicinal products for human use, defines a multi-centre clinical trial (MC-CT) as a CT conducted according to a single protocol but at more than one site, and therefore by more than one investigator. The trial sites may be located in a single Member State (MS), in a number of MS, or in one or more MS and additionally in third countries. This document relates to a MC-CT with trial sites in several MS, referred to as multinational CTs (MN-CTs) throughout this document.
In the context of the implementation of Directive 2001/20/EC and with the aim to harmonise the conduct of CTs within EU MS, the EU-Commission has issued detailed guidances and information regarding major aspects of clinical trials, such as the format of requests to Competent Authorities (CA) and of CT information to be submitted to Ethics Committees (EC), the reporting of adverse reactions arising from CT, the documentation on the quality of the Investigational Medicinal Product (IMP) and the European clinical trial database EudraCT (EudraLex - Volume 10 Clinical trials guidelines).
To coordinate the implementation of Directive 2001/20/EC across the MS at an operational and national level, the EU Heads of Medicines Agencies have set up the Clinical Trials Facilitation Group (CTFG). This is another major step for the achievement of harmonisation of CTs in Europe.

With the translation of the Directive into national laws and regulations, divergent practices between the different MS remain in areas such as:

- Distribution of duties between the CAs and the ECs
- Content, format or language requirements
- Timelines for the review of a CT application
- Different application dates by the sponsor in the different MS
- Human resources and workload vs. the number of applications per NCA

Regarding a MN-CT, for which an application is filed in several MS as the authorisation of a CT is subject of national legislations, the assessment of the same Clinical Trial Application (CTA) for a given MN-CT might result in varying final decisions. Country-specific modifications might occur due to changes requested by the different NCAs and ECs; a CT might even be approved in one MS and rejected in another. Such situations not only may jeopardize the scientific value of clinical trial results due to country-specific modifications but also are hardly understood by the public, since the levels of protection of clinical trials participants should be the same in all European countries.
Further to October 2007, CTs Conference organised by the European Commission and EMEA, the importance of maintaining the following general principles for the conduct of clinical research in the European Union has been recognised:

- Protect clinical trials participants
- Ensure high-quality research in the EU
- Contribute to a favourable research environment in EU
- Bring innovative medicines to patients as quickly as possible

For these reasons, the need to harmonise MN-CTs in Europe in order to ensure the protection of participants as well as the scientific value of CTs by the means of harmonising NCAs' processes and practices relating to MN-CTs (about 30% of CTs in EU), has become a priority for the CTFG. Thus, the organisation of coordinated assessment of multinational CTAs through the Voluntary Harmonisation Procedure (VHP) has been

a major objective of the CTFG work plan for 2008-2010. This procedure has been set up within the current legal frame-work for CTs.

On the basis of the experience with the VHP in 2009, the CTFG developed a new version of the VHP: the procedure has been modified in order to streamline the assessment, to enlarge the scope of the pilot phase and to shorten the timelines. For each VHP, one of the participating NCA takes the lead in the scientific consolidation of the letter with grounds for non-acceptance.
Procedures as for example assessment reports and rapporteurships from the decentralised procedure are discussed to be included in the VHP.

4 Scope and general principles

On the one hand, a harmonisation procedure of the assessment occurring after the application of a CT in the different MS is foreseen difficult to achieve and may even be counterproductive by adding an additional step at the end of an already lengthy process. On the other hand, taking into account the current legal framework, each NCA remains responsible for the approval of a CTA in its own country. Therefore, a harmonisation procedure for the assessment of MN-CT applications is proposed i) before the initial phase of the national process, and ii) on a voluntary basis.
The NCAs will be giving CTAs involving First in human (FIH)[1] or with "critical" products,[2] and the VHP in general, a priority in their daily work.

The main objectives of the assessment of the CT are to ensure the quality of the IMP and the safety of the trial subjects.

Due to the volume of MN-CTs to be assessed every year and bearing in mind that CTA decisions remain a competence of each NCAs, an incremental process is proposed with an initial pilot phase.

During the pilot phase, all MN-CTs involving not less than 3 MS are eligible to undergo the VHP.

During the pilot phase no fees will be charged for VHPs or VHP-SA; the costs of the NCAs will be covered by the national applications to the NCAs.

5 Definitions

- VHP-Coordinator (VHP-C): the CFTG representative of the NCA in charge of coordinating the VHP for CTAs

[1] First in human (FIH) MN-CTs and particularly CTs with investigational medicinal products with known or anticipated risk factors as described in EMEA/CHMP/SWP/294648/2007
[2] investigational medicinal products (limited community expertise e.g. IMP with novel mode of action, novel manufacturing process, novel administration and storage requirements, links to a class of medicinal products with recognised safety concerns, unresolved pre-clinical abnormal findings, for instance monoclonal antibodies interfering with immune regulation, and advanced therapies) or "critical" MN-CTs (e.g. for limited trial populations e.g. orphan diseases, less common types of cancer, paediatric diseases with small numbers of participants, diseases with small numbers of participants or unmet medical needs), based on NCA's judgement and endorsed by the CTFG

- Participating NCAs (P-NCAs): the NCAs concerned by the CT and wishing to participate to the VHP on a voluntary basis

- The “VHP applicant”: a sponsor, whoever is submitting a request for VHP of a MN-CT to the CTFG

- Request for VHP: the letter from the VHP applicant, requesting a planned MN-CT to undergo the VHP. The applicant should describe the key features of the CT and indicate which EU countries will be involved in the MN-CT. The request for VHP should also contain all the documentation required for the assessment of the CTA through the VHP. The content of the VHP application is detailed under section “Format and content of the VHP application”

- Leading NCA: The NCA responsible for coordinating the response to the applicant.

6 Outline of the proposed procedure

The VHP will comprise three phases:

- Phase 1: Request for VHP and validation of the application
- Phase 2: Assessment step: review of a CTA by the NCAs of the participating MS
- Phase 3: National step, with formal CTAs to all concerned NCAs

Phase 1 and 2 are actually composing the submission phase to the CTFG. Phase 3 is the formal submission of a CT to each NCA according to the national regulations.

6.1 Request for VHP and validation of the application

In the request for VHP, the applicant should shortly describe the key features of the CT and indicate which EU countries will be involved in the MN-CT. The request for VHP should also contain all the documentation required for the assessment of the CTA by the MS.

6.1.1 At any time, the applicant informs the VHP-C by sending the request for VHP to VHP-CTFG@VHP-CTFG.eu via E-mail/Eudralink, highlighting important features of the MN-CT and the documentation required for the assessment of the CTA

6.1.2 Upon receipt of the request and VHP-documentation, the VHP-C creates a new file in the VHP database and allocates a VHP number

6.1.3 The complete VHP-documentation is forwarded electronically by VHP-C to the P-NCAs immediately after receipt

Within 5 working days after receipt, the VHP-C informs the applicant whether all requested MS will participate. Validation of the dossier will also be performed and the applicant will be informed of any deficiencies or, if complete, the start date of the VHP.

All timelines in the VHP are calendar days with one exception: the 5 working days between initial submission and confirmation by the VHP-C (0) and the 5 working days when submitting VHP-substantial amendment (VHP-SA)(7.1).
In those MS declining participation in the VHP, a national CTA in parallel to the VHP or after the VHP is possible.

6.2 VHP CTA assessment step

Of note, the timelines proposed hereby are maximum timelines. Whenever possible for the P-NCAs, the timelines can be shorter.
Important: during the entire VHP, any contact from the applicant to the P-NCA should be avoided and the VHP-C being the only contact for the applicant to ensure that all P-NCA receive identical information.

6.2.1 VHP Assessment Step I (Day 1-Day 30)

- In the absence of grounds for non acceptance (GNA)/ request for further information (RFI),
  - a statement will be sent by the VHP-C to the applicant (copy to all P-NCAs), not later than day 30, stating that no GNA/RFI have been expressed by any P-NCA during the VHP assessment phase and that the P-NCAs unanimously consider the CTA (with date & version #) acceptable for this MN-CT
  - The final step, i.e. submission of a CTA in each participating MS, can then start (See Section 6.3 National step)

- In case of GNA/RFI:

- A consolidated list of GNA will be forwarded to the applicant by the VHP-C via E-mail/Eudralink on day 30 with a request for response to the GNA/RFI and/or for the revised CT documentation by E-Mail/Eudralink by day 40 at the latest
- If the applicant decides to proceed, the VHP assessment step II starts on receipt of the responses together with a revised CT documentation by the VHP-C.
- The VHP file will be closed with a notice to the applicant and the P-NCAs if no response from the applicant is received within the allotted time

6.2.2 VHP Assessment Step II (Day 40-Day 60)

The applicant's response document is immediately dispatched by the VHP-C to all P-NCAs for review. After a 7-day period, the VHP-C compiles the P-NCAs assessments.

➢ If consensus is achieved, i.e. the revised version of the CTA is considered approvable by all P-NCAs on day 50, the VHP-C sends to the applicant a statement by electronic mail (copy to all P-NCAs), mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the revised CTA (with date & version #) as approvable.
The final step, i.e. submission of a CTA at each participating NCA, can start (See Section 6.3 National step).
➢ If no consensus is among the P-NCAs a teleconference will be organised (between day 50 and day 57), during which all P-NCAs are invited to express their views and possible solutions to the remaining issues so that a final decision can be given at the end of the meeting:
- Unanimous decision of the MS that the revised version of the CTA is approvable: an electronic letter to the applicant will be sent on day 60, mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the re-

vised CTA (with date & version #) as approvable. Comments to facilitate the national submission in the MS might be added. The final step, i.e. submission of a CTA in each participating MS can start (See Section 6.3 National step).

- Unanimous decision of the MS that the revised version of the CTA is not approvable: an electronic letter will be sent to the applicant on day 60 with the remaining GNAs and proposed solutions for national submissions or a VHP-resubmission. Comments to facilitate national submissions in the MS or a VHP-resubmission might be added (See Section 6.3 National step).
- In the case that not all P-NCA agree, that all GNA/RFI have been resolved, the open points and the names of MS, which consider GNA/RFI as unsolved, will be forwarded to the applicant. Also the list of MS, which consider all GNA/RFI as resolved, will be forwarded. The open points have to be resolved before or in the national procedure, the timelines for the submission of the CTA (20 days, see Section 6.3) and the approval by the NCA (10 days, see Section 6.3) do not apply for the MS with unsolved GNA.

6.3 "National step" Formal CTA

The acceptability statement following the VHP does not imply that the MN-CT is authorised by the P-NCAs. Once the applicant has been notified that the CTA is considered acceptable (at the end of the VHP assessment Step I or II), a CTA has to be submitted in each participating MS as outlined in the Clinical Trial Directive (2001/20/EC) and in the *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (ENTR/F2/BL D 2003. current version)*.

In his covering letter for the CTA, to the NCAs the sponsor should remind the NCAs that this MN-CT has undergone the VHP and add the E-Mail with the VHP approval. Generally, no changes between the final CTA and the CTA approved during the VHP will be accepted.

However, if at the end of the VHP process, a NCA has considered GNA as unsolved or if the solutions proposed by that NCA are not acceptable for the sponsor, the sponsor may decide to skip the filing of a CTA in that MS.

Or, if the sponsor decides to apply in a MS that was initially not part of the VHP, the NCA of the new MS may accept the decisions taken in the VHP, without changes by the sponsor to the documents that have been agreed in the VHP.

Submissions of the CTA to the NCAs should not be later than 20 days after receipt of the VHP acceptability statement by the applicant.

It is agreed by the MS, that after a positive VHP a decision of the NCA should be issued within 10 days and that no scientific discussion on the agreed documents of the VHP (e.g. Protocol, IB, IMPD) will be started again.

The applicant should notify a list of the dates of authorisation of the MN-CT to the VHP-C, when available.

7 Substantial amendments

Substantial amendments (SA) of CTAs that have undergone a VHP can be submitted to the VHP-C at any time, under the condition, that the CTAs have already been approved by the P-NCAs. The date of the national approvals should be given in the cover letter together with summary information on the content of the SA.
The notification should be made in accordance with the current version of the *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.* The amendment form of annex 2 of the guideline should be used and appropriate documents to assess the changes of the CT should be added. To facilitate the assessment of the changes, all changed documents (e.g. IMPD, IB and Protocol) should be submitted with the changes highlighted or with a comparative table before-after. When changes are complex and affecting several parts of the document, the complete document with track changes as well as a clean copy with the final version should be submitted.
Like the documents of the original VHP, SAs should be submitted via E-Mail to the VHP-C.

7.1 Timelines of substantial amendments

The submission of SAs to the VHP-C is possible at any time. Within the 5 working days after the submission, the submitted documentation will be validated and the applicant will be notified via E-mail of any deficiencies or of the start of the VHP-SA. If the Dossier is not complete, additional information will be requested by the VHP-C and this should be submitted by the applicant within 3 days.
The result of the assessment will be communicated to the applicant within 20/35 days after a valid request. In case of a rejection, the reasons (GNA) will be sent to the applicant. GNA can not be addressed during the VHP-SA by the applicant, but a resubmission addressing the GNA with the shorter timeline for approval (20 days) is endorsed.
In case of a positive statement by the VHP-C, the applications to the P-NCA should be filed according to the national regulations within 10 days. The approval by the NCA should be issued within 7 days after the valid request (see the flow chart on VHP-SA for detailed timelines).

8 References

- 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. Official Journal L 121, 01/05/2001. p34 – 44
- 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. ENTR/F2/BL D (2003) Rev 2 or newer versions
- Detailed guidance on the European clinical trials database (EUDRACT Database) as required by Article 11 and Article 17 of Directive 2001/20/EC, CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset. April 2004
- Guideline on strategies to identify and mitigate risks for first-in-man human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/294648/2007

9 Appendices

9.1 Flow-charts

9.1.1 Flow chart Voluntary Harmonisation Procedure

Phase 1	Request for VHP	
Any time	Electronic submission of request and CTA documentation to VHP-C via E-Mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the CTA documentation to the P-NCA	
Within 5 working days after receipt at VHP-C	Information to the applicant on the acceptance by NCAs and on the date of start (DAY 1) of the VHP phase 2 Or, Compilation of formal deficiencies of the VHP dossier, if applicable: if needed, the missing information will be requested by the VHP-C and should be submitted within 3 days	
Phase 2	VHP CTA assessment step I	
Day 1	Start of VHP	
Day 30	If no GNA or RFI: information (VHP-C) of the applicant on acceptance	End of VHP and start of phase 3 →National step
Day 30	In case of GNA and/or RFI: transfer of GNA/RFI by VHP-C to the applicant and the P-NCAs (Response has to be submitted within 10 days)	
	Day 40 – Day 50 VHP assessment step II	
Day 40	Deadline for electronic submission of additional documentation and revised CTA to VHP-C by the applicant	
Day 50	If the revised CTA is considered approvable: information (by the VHP-C) of the applicant on acceptance	End of VHP and start of Phase 3 →National step
Day 60	If a revised CTA approvable after internal discussion : - Information of the applicant by the VHP-C on acceptance	End of VHP and start of Phase 3 → National step
	Revised CTA not approvable : - End of the VHP: Letter to the applicant with details of GNAs	
	Disagreement between MS on GNAs: - List of MS that are ready to approve the CTA and list of MS with open points	
Phase 3	National step	
Within 20 days of receipt of approvability statement	Submission of the formal CTA (as agreed during the VHP with the requested changes, where applicable) to each P-NCA with the letter of decision on VHP	
Within 10 days of valid CTA[3] After P-NCA's decision	Procedure and decision according to national laws Information of the VHP-C by the applicant on the outcome of the national CTAs (with respect to the VHP decisions)	

[3] The 10 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.

9.1.2 Flow chart VHP of substantial amendments (VHP-SA)

Phase 1	Request for VHP-SA	
Any time	Electronic submission of request and substantial amendment documentation to VHP-C via E-mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the SA to the P-NCA	
Within 5 working days after receipt at VHP-C	Information to the applicant on the date of start of the VHP-SA phase 2,. Or, Compilation of formal deficiencies of the VHP-SA dossier, if applicable (if needed the missing information will be requested by the VHP-C and should be submitted within 3 days)	
Phase 2	VHP-SA CTA assessment step	
Day 1	Start of the VHP for substantial amendments	
Day 20	If no GNA within the assessment of the VHP-SA were raised by the P-NCA: information (via VHP-C) of the applicant on positive decision	End of VHP SA and start of phase 3 →National step
Day 35	If GNA existed, but were resolved after internal discussion: information (via VHP-C) of the applicant on positive decision	End of VHP SA and start of phase 3 →National step
Day 35	In case of rejection: transfer of reasons (GNA) by VHP-C to the applicant and the P-NCAs.	
Phase 3	National step	
Within 10 days of receipt of approvability statement	Submission of the formal substantial amendment to every P-NCA including the letter of decision on VHP SA	
Within 7 days of valid SA[4] After P-NCA's decision	Procedure and decision on SA according to national laws Information of the VHP-C on the outcome of the national CTAs (with respect to the VHP SA decisions)	

Shorter timelines are possible for resubmissions

[4] The 7 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.

9.2 Content of a "Request for VHP"

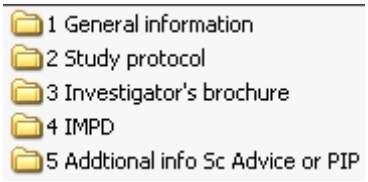
The following information should be contained in a request for VHP:

1. Covering letter including the EudraCT number and a short description of the key features of the CT

2. List of the NCAs the applicant intends to submit a CTA in the national phase
3. core CTA EudraCT form~~, (~~common information for all MS~~)~~
4. Protocol related folder with study protocol including synopsis
5. Investigator's brochure

6. IMP dossier, as defined in EudraLex - Volume 10 (including viral safety and IMPD on the Placebo, if applicable)
7. IMP additional information (if not included in IMPD): manufacturing authorisation; GMP compliance certificate; importation authorisation; certificate of analysis, if applicable; authorisation for special characteristics of products e.g. GMO or radioelements.
8. NIMPs Dossier according to ANNEX I, if applicable
9. Copy/summary of any scientific advice from any competent authority or EMEA and PIP summary, if applicable

For FIH MN-CTs, all applicable clinical and non-clinical aspects specific to the product under investigation and their potential impact on the study design and/or on the conduct of the clinical trial should be discussed, as outlined in the Guideline on strategies to identify and mitigate risks for FIH-CTs with IMP (EMEA/CHMP/SWP/294648/2007), or justification should be provided as to why the points have not to be addressed in the CT documentation.
Electronic structure of the VHP application:



10 ANNEX I

10.1 HARMONISED REQUIREMENTS FOR NON INVESTIGATIONAL MEDICINAL PRODUCTS IN CTA SUBMISSIONS

Within the design of a clinical trial, there may be the use of components other than Investigational Medicinal Products (IMPs). Examples of such other products are rescue medication, challenge agents and background therapy. Such products are referred to as non-investigational medicinal products – NIMPs. The definition of a NIMP is provided in Chapter III of Volume 10 of The Rules Governing Medicinal Products in the EU (Guidance on Investigational medicinal products (IMPs) and other medicinal products used in Clinical Trials).

The status of such products has been addressed in Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU and in Commission guidance (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 safeguarding of the clinical trial subject, in accordance with Article 3 of Directive 2001/20/EC and the objectives of this Directive in general, is ensured *inter alia* by guaranteeing the quality and safety of the products and substances used in the trial. As NIMPs do not fall within the definition of investigational medicinal products, Articles 13 and 14 of Directive 2001/20/EC are not directly applicable. To meet the requirements of Article 3(2) of Directive 2001/20/EC, and as referred to in Article 6(3) relating to the protection of the trial subject, the same level of quality and safety should be ensured for the NIMPs as for the IMPs used in the trials. Information on the ways in which sponsors can ensure the quality of the NIMP in terms of the appropriateness of the manufacturing site is included in Annex 1.

The Commission guidance strongly recommends that, where possible, non-investigational medicinal products (NIMPs) have a marketing authorisation in the Member State where the trial is being conducted. Where this is not possible, the next choice would be a product which has a marketing authorisation in an other EU Member State. On a case-by-case basis, it may be possible for sponsors to justify the use of NIMPs obtained from an ICH region [USA. Japan] or from a Mutual Recognition Agreement-partner country [Australia, Canada, New Zealand, Switzerland]. A Mutual Recognition Agreement provides assurance that equivalent GMP standards are applied by both parties of the agreement. In line with the approach in the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004, the data requirements to support the use of products from these countries are reduced.

The sponsor should provide details of the NIMPs and their proposed use in the trial protocol. Information on the NIMP should be provided in accordance with the guidance provided below. To facilitate the preparation of a harmonised dossier, documents submitted to the Competent Authority may be submitted in English.

The sponsor is responsible for implementing a system to ensure that the trial is conducted and data are generated in accordance with the principles of Good Clinical Prac-

tice. To comply with these principles, a trial has to be conducted according to the protocol and all clinical trial information should be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified. In this context, the sponsor should implement a system allowing traceability of medicinal products which allows adequate reconstruction of NIMP movements and administration, taking into account the purpose of the trial and trial subjects' safety. It has at least to include a procedure, established with the investigator and if applicable, with the hospital pharmacy, to record which patients received which NIMPs during the trial with an evaluation of the compliance.

1. BACKGROUND THERAPY/RESCUE MEDICATION

Background therapy

This type of medicinal product is administered to each of the clinical trial subjects, regardless of randomisation group, to treat the indication which is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication in the Member State concerned. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared to an active comparator or to placebo plus background treatment. Sponsors should note that the Commission guidance strongly recommends that, where possible, non-investigational medicinal products (NIMPs) have a marketing authorisation in the Member State where the trial is being conducted. Where this is not possible, the next choice would be a product which has a marketing authorisation in an other EU Member State. In situations where the background therapy does not have a marketing authorisation in the Member State where the trial is being conduction, a justification for its use should be provided.

Rescue medication

Rescue medications are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.

The following examples lay out the contents of the NIMP dossier where the NIMPs are used as background therapy or rescue medication.

1.1 NIMP is a marketed medicinal product in the concerned Member State

Simplified dossier is required containing

- copy of the SmPC
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

1.2 NIMP is a marketed medicinal product in an other EU Member State

Simplified dossier is required containing

- copy of the SmPC (translated as necessary)

- information on any repackaging and/or relabelling and a list of sites involved
- acceptable evidence of GMP compliance [manufacturer's authorisation/QP certification for non-EU sites] for the repackaging and/or relabelling or a justification for its absence
- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in an other EU Member State is used in the trial
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

1.3 a NIMP is a marketed medicinal product in an ICH country or a country which has Mutual Recognition Agreement (MRA) with the EU

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC or local equivalent (translated as necessary)
- information on any repackaging and/or relabelling and a list of sites involved
- acceptable evidence of GMP compliance [manufacturer's authorisation /QP certification for non-EU sites]for the repackaging and/or relabelling or a justification for its absence
- importer's authorisation
- justification for the use of the product if there is a comparable product authorised in the concerned Member State or an other EU Member State but one with a marketing authorisation an ICH /MRA country is used in the trial
- justification for the use of the product if there is no comparable product licensed in the concerned Member State or it is used outside of its marketing authorisation in the ICH/MRA country
- justification for the safe and effective use of the product in the trial, including any potential for interactions between the NIMP and the IMPs to be used in the trial,
- confirmation of reduced testing (e.g. identity) by analytical testing or an alternative appropriate method

1.4 NIMP is a marketed medicinal product in a third country (not ICH or MRA country)

Full dossier is required containing

- documents on quality and manufacturing as per the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004
- results from non-clinical and clinical studies
- acceptable evidence of GMP compliance including the site of batch release by a Qualified Person (QP)
- manufacturer's authorisation/importer's authorisation
- justification for the safe and effective use of the product in the trial taking into account any potential for interactions between the NIMP and the IMPs to be used in the trial and if it is used outside of its marketing authorisation

- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in a third country is used in the trial

1.5 NIMP has no marketing authorisation (is manufactured specially for use in the proposed trial) but the drug substance is contained in a medicinal product marketed in the concerned Member State or an other EU Member State

Full dossier is required containing

- documents on quality and manufacturing as per the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004
- acceptable evidence of GMP compliance including site of batch release by QP
- manufacturer's authorisation/importer's authorisation
- justification for the safe and effective use of the product in the trial

1.6 NIMP is defined in the protocol but is not fixed to a particular product

In this situation, the product(s) to be used is/are authorised in the Member State in which the trial is being undertaken but a particular brand is not specified in the protocol.

This information should be included confirmed in the covering letter. No additional information is required.

2. CHALLENGE AGENTS/ MEDICINAL PRODUCTS USED TO ASSESS END-POINTS

Challenge agents

Challenge agents are usually given to trial subjects to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed. They may be substances without a marketing authorisation, however some have a long tradition of clinical use.

Medicinal products used to assess end-points

This type of NIMP is given to the subject as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.

The following examples lay out the contents of the NIMP dossier where the NIMPs are used as challenge agents or as medicinal products used to assess end-points.

2.1 NIMP is a marketed medicinal product in the concerned Member State

Simplified dossier is required containing

- copy of the SmPC
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

2.2 NIMP is a marketed medicinal product in an other EU Member State, in an ICH country or in a country which has a Mutual Recognition Agreement with the EU

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC [or equivalent document] translated as necessary
- information on any repackaging and list of sites involved
- acceptable evidence of GMP compliance for the modification (including repackaging) - manufacturer's authorisation/QP certification (for non-EU sites) or justification for its absence
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial
- reduced testing (e.g. identity) by analytical testing or an alternative appropriate method
- importer's authorisation for ICH/MRA marketing authorisations
- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in an other EU Member State, ICH country or MRA country is used in the trial

2.3 NIMP is a marketed medicinal product in an other EU Member State, in an ICH country or in a country which has a Mutual Recognition Agreement with the EU but has been modified for use in the trial

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC [or equivalent document] translated as necessary
- information (as per chapter 4 of the *Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials* - CHMP/QWP/185401/2004) on any modification to the product and list of sites involved
- acceptable evidence of GMP compliance for the modification - manufacturer's authorisation/QP certification (for non-EU sites) or justification for its absence
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial
- reduced testing (e.g. identity) by analytical testing or an alternative appropriate method
- importer's authorisation for ICH/MRA marketing authorisations
- justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in an other EU Member State, ICH country or MRA country is used in the trial

2.4 NIMP is an unlicensed product previously authorised for use as a NIMP in a trial conducted in the concerned Member State by the same sponsor or where a letter of access to the data from the sponsor of the previous trial is available

Simplified dossier is required containing

- EudraCT number of previous trial
- confirmation that the trial population is in line with that of the previously approved trial or justification of any differences
- confirmation that the dose/duration of dosing does not exceed that of the previously approved trial or justification of any differences
- justification for the safe use of the product in the trial including any potential for interactions between the NIMP and the IMPs to be used in the trial
- confirmation that there were no safety or quality issues arising from the use of this product in the previous trial
- confirmation that the product is manufactured and controlled (including formulation, site of manufacture, quality control and specifications) in line with the conditions of the previously approved trial taking account of both the initial NIMP dossier and any subsequent amendments

2.5 NIMP is an unlicensed product which has been used as an IMP in a previous trial conducted in the concerned Member State by the same sponsor or another sponsor where a letter of access to the data from this sponsor is available

Simplified dossier is required containing

- EudraCT number of previous trial
- confirmation that the trial population is in line with that of the previously approved trial or justification of any differences
- confirmation that the dose/duration of dosing does not exceed that of the previously approved trial or justification of any differences
- justification for the safe use of the product in the trial including any potential for interactions between the NIMP and the IMPs to be used in the trial
- confirmation that there were no safety or quality issues arising from the previous trial
- confirmation that the product is manufactured and controlled (including formulation, site of manufacture, quality control and specifications) in line with the conditions of the previously approved trial taking account of both the initial IMP dossier and any subsequent amendments

2.6 NIMP is an unlicensed product where the active moiety has been previously administered to humans

Simplified dossier is required containing

- rationale for its safe use in the trial including information on the extent of previous human exposure, including any potential for interactions between the NIMP and the IMPs to be used in the trial
- evidence that existing nonclinical safety data support the use in the proposed trial

- information on the composition, method of manufacture and controls applied to the product
- confirmation of the site of manufacture of the product
- confirmation of the appropriateness of the manufacturing site (eg a copy of the manufacturer's authorisation/EU QP declaration/ importer's authorisation)
- confirmation of the mechanism for ensuring the quality of the product (eg QP release)

Annex 1

EVIDENCE OF APPROPRIATENESS OF THE MANUFACTURING SITE AND MECHANISM FOR CONTROLLING QUALITY OF THE PRODUCT

Acceptable evidence of the appropriateness of the manufacturing site and the mechanism for controlling the quality of the product includes, but is not limited to, the following

1. Manufactured under the provisions of a manufacturer's authorisation for the manufacture of marketed products or IMPs and QP released
2. Manufactured under national provisions to the principles of GMP and released for use by an appropriately experienced individual