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Comments on the Quality Part

Susanne Keitel and Hans-Joachim Janhsen

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Background and Introduction

The Clinical Trials Directive (2001/20/EC) came into force in April 2001, harmonising the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for human use. Member States were obliged to transform the requirements outlined in the Directive into the respective national laws by May 2004. The Directive introduced a harmonised procedure for the authorisation to perform a clinical study in any one of the EU Member States. In addition, it defines the documentation to be submitted to the Ethics Committee as well as the Investigational Medicinal Product Dossier (IMPD) to be submitted to the competent authority for approval. Thus, an IMPD is requested whenever the performance of a clinical study in any one of the EU Member States is intended.

In July 2006, the European Commission published the new volume 10 of the Rules governing Medicinal Products in the European Union (EudraLex) "Clinical Trials – Notice to Applicants". This first edition summarises legal and regulatory requirements for the conduct of clinical studies in the EU. It contains background information and provides links to guidance documents on various aspects of clinical trials, from the application form to the qualification of GCP inspectors.

It is the intention of this document to summarise and explain the requirements for the quality part of the IMPD. It is not intended to provide a complete summary of the requirements described in the respective guideline, but rather to highlight and explain specific aspects. Detailed aspects of the authorisation procedure itself are described in Volume 10 and published by the respective competent authorities of the Member States.

An IMPD is required for every Investigational Medicinal Product (IMP) to be used in a clinical study, regardless of whether it is the test product itself, a reference product already authorised or a placebo. The IMPD includes summaries of information related to the quality, manufacture and control of the IMP, data from non-clinical studies and from its clinical use. An overall risk-benefit assessment, critical analyses of the non-clinical and clinical data in relation to the potential risks and benefits of the proposed study have to be part of the IMPD. In certain situations, e.g. where the IMP has already been authorised as a medicinal product in one of the EU Member States or where clinical studies with the IMP have already been approved by a Member State, a simplified IMPD will be sufficient. In line with the Clinical Trial Directive, the EU Commission has published explanatory documents outlining the details of the procedures involved in applying for an authorisation of a clinical study. Guidance document ENTR/CT1 "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" provides basic information on the application format and contents of an application for a

clinical trial and the IMPD. ENTR/CT2 gives guidance for the application for an Ethics Committee opinion. Both documents are included in Volume 10 of EudraLex.
The data in the IMPD should follow the headings and order provided in the Commission document ENTR/CT1, i.e. they should follow the principle of the Overall Summaries and Overviews of the Common Technical Document CTD. ENTR/CT1, however, contains the disclaimer that the headings "are not mandatory nor are they an exhaustive list…. If there is no appropriate heading, a new section may be added…. It is impossible to formulate detailed guidance to cover all situations. Sponsors are advised to use this detailed guidance as a starting point in their preparation of data packages for submission. In addition, the relevant Community guideline or European Commission decision should be followed for specific types of investigational medicinal product, clinical trial, or patient group…".

The Quality Part of an IMPD

As the situation in the different EU Member States regarding requirements for the authorisation of clinical studies was rather heterogeneous prior to adoption and implementation of the Clinical Trials Directive, industry has been concerned about possibly divergent interpretations of the new requirements by the different Member States. A consistent and common-sense interpretation by competent authorities, however, is of vital importance in order to make and keep the EU an attractive location for the conduct of clinical trials. As a consequence, the EU Commission gave the Joint CHMP/CVMP Quality Working Party (QWP) the mandate for drafting a guideline on the requirements to the quality part of an IMPD. A concept paper for a Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials was published in April 2004, a first draft of the related guideline was published for comments by interested parties in December 2004. Following extensive discussions and consultations amongst Member States and with interested parties, the guideline has been finalised by QWP earlier this year. The final version has been published in Chapter III "Information on the quality of the investigational medicinal product" of Volume 10 of EudraLex. The following text highlights important aspects of the guideline. For more detailed information, reference is made to the guideline. Text that has been taken literally from the guideline is marked in italics.

In its introductory section, the guideline states that clinical trial applications are significantly different from marketing authorisation applications. *Whilst the latter ones have to ensure a state-of-the-art quality of a product for wide use in patients, information to be provided for IMPs should focus on the risk aspects and should consider the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself.* As a consequence, it is not possible to define very detailed requirements applicable to all sorts of different products. However,

the guideline aims at providing guidance on standard information which should normally be presented in the quality part of an IMPD.

When compiling the quality part of the IMPD for phase II and phase III clinical studies, the larger and longer exposure of patients to the product have to be taken into account compared to phase I clinical studies. Based on the diversity of products to be used in the different phases of clinical trials, the requirements defined in the guideline can only be of an illustrative nature and can not be expected to present an exhaustive list. IMPs based on innovative and/or complex technologies may need more detailed data to be submitted. For certain situations, e.g. where the drug substance from the specific source to be used for an IMP is already included in a medicinal product authorised within the EU, not all the documentation need to be submitted in the IMPD, but a simplified IMPD as described in the document "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/CT) will suffice.

In order to also facilitate manufacture of clinical supplies intended for the use in the EU and a different region, the guideline allows reference to either the European Pharmacopoeia (Ph.Eur.), the Pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) for active substances and excipients. However, for active substances, the suitability of the referenced monograph to adequately control the quality of the active substance (impurity profile) has to be demonstrated by the applicant/sponsor. This flexibility in choice as regards pharmacopoeial standards is very much in contrast to the situation an applicant will face in any marketing authorization application where reference to Ph. Eur. is legally binding in the EU. Thus, any sponsor of a clinical trial who chooses to refer to a USP or JP monograph in the presence of a Ph. Eur. Monograph should be aware of the requirements he will face in any subsequent marketing authorization application. The guideline therefore advises that for generic bioequivalence studies that are intended to support a Marketing Authorisation Application (MAA), reference to the Ph. Eur. will facilitate future licensing activities in the EU.

For impurities in IMPs, ICH impurity guidelines are not applicable due to the different exposure of volunteers/patients to the IMP compared to the exposure of long-time patients to authorized medicinal products. Therefore, the justification of the product's safety as regards impurities is with the sponsor who needs to consider the intended use and anticipated exposure of volunteers and patients in his risk assessment. Another significant difference between IMPD and MAA requirements can be observed in the grade of detail requested for the description of analytical methods. While in a MAA a detailed description of the analytical procedures is requested, the description of the analytical method as such will suffice in an IMP (see ICH Q 2 (A) for definitions: "analytical procedure" refers to the way of performing the analysis, "analytical method" refers to the principles of the method used).

I. GENERAL REQUIREMENTS

Active Substance

Same as for a MAA, there are three different ways to provide the information on the active substance:

- reference to an Active Substance Master File
- submission of a Certificate of Suitability (CEP) of the European Directorate for the Quality of Medicines (EDQM)
- submission of the information in the IMPD.

A description of the different procedures can be found in the "Guideline on Active Substance Master File Procedure – CPMP/QWP/227/02 Rev 1" and the "Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1"

IMPURITIES

For substances which comply with a monograph of the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required once the suitability of the monograph to adequately control the quality of the active substance has been demonstrated. In all other cases, however, impurities, degradation products and residual solvents deriving from the manufacturing process or starting materials relevant to the drug substance used for the clinical trial, should be stated. As outlined above, justification of the level of impurities specified is up to the sponsor.

ANALYTICAL PROCEDURES

For all tests included in the specification of the active substance, the analytical methods should be described (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC, etc.). It is **not** necessary to provide a detailed description of the analytical procedures. For substances which comply with a monograph of the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP, reference to the relevant monograph is acceptable.

VALIDATION OF ANALYTICAL PROCEDURES

Regarding validation of analytical procedures, the guideline foresees a step-wise approach with more information being requested for later stages in clinical development which also include a larger number of patients and longer exposure times. While for phase I clinical trials, confirmation of the suitability of the analytical methods used is sufficient, demonstration of the suitability is required for phase II and III clinical tirals. For phase I, the acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form while for phases II and III, a summary of the results of the validation which has been carried out

will be requested. However, there is no need to provide a validation report for any clinical trial application. This requirement is only applicable to MAAs. In addition, for substances which comply with a monograph of the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP, reference to the relevant monograph is sufficient. In this case, there is no need for any validation data in the IMPD.

Stability

The active substance stability data available at the respective stage of development should be summarised in tables. This should include identification of those parameters known to be critical for the stability of the active substance, i.e. chemical and physical sensitivity, e.g. photosensitivity, hygroscopicity. Whenever possible, it will be helpful to describe potential degradation pathways known to the sponsor. Again, there is a reduced degree of information requested for active substances complying with a pharmacopoeial monograph. In this case, confirmation that the active substance will meet specifications at the time of use is sufficient.

Investigational Medicinal Product Under Test

Description and Composition of the Investigational Medicinal Product

In order to allow an assessment of the IMPs quality, the qualitative and quantitative composition of the IMP needs to be provided, including a short statement or a tabulation of the dosage form and the function of each excipient.

Pharmaceutical Development

This section is limited to a short description of formulation development, including justification of any new pharmaceutical form or excipient in the IMP. The guideline explicitly states that for early development, there may be no or only limited information to include in this section.
However, if changes in the formulation or dosage form compared to the IMP used in earlier clinical trials are made in a subsequent clinical phase, the relevance of the earlier material compared to the product under testing should be described. *Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.*

Manufacturing Process Development

Changes in the current manufacturing process compared to the one used in phase I and phase II clinical trials, respectively, are to be explained. Again, the focus should lie on dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

Process Validation and/or Evaluation

In line with the requirements for MAAs, data on process validation are not required during the development phases, i.e. clinical phases I to III, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP and non-standard manufacturing processes. *In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.*

Control of Excipients

Specifications

Whenever reference to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP can be made, there are no further requirements. *For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided.*

Analytical Procedures

In line with the requirements for the active substance, there is no need to submit a detailed description of analytical procedures. Only in cases where reference to a pharmacopoeial monograph listed above cannot be made, the analytical methods used should be indicated.

Validation of the Analytical Procedures/Justification of Specifications

At no stage in the clinical development process is there a need to provide validation data for the analytical procedures used to control the quality of excipients in the IMPD. Similarly, there is no need to justify the specification of an excipient.

Excipients of Animal or Human Origin

Based on the risk inherent to the use of excipients of animal or human origin, detailed requirements for these types of excipients are outlined in section 7.2.1.A.2. of the guideline.

Novel Excipients

Same as for MAAs, there is a need for more detailed information in case of the use of novel excipients, i.e. excipients not hitherto used in human medicinal

products. Details are to be given on their manufacturing process, characterisation and control in relevance to product safety. *Information as indicated in section 3.2.S of the CTD should be provided. Consistent with the respective clinical phase (c.f. section 7.2.1.A.3 of the guideline), details are to be included on e.g. their manufacturing process, characterisation and stability.*

Control of the Investigational Medicinal Product

Specifications

The release and shelf-life specifications set by the sponsor should be submitted, including test methods and acceptance criteria. *Upper limits may be set for both individual degradation products and the sum of degradation products. Safety considerations should be taken into account, the limits should be supported by the impurity profiles of batches of active substance used in non-clinical/clinical studies.* As more information becomes available as the clinical trial program progresses, the specifications and acceptance criteria should be reviewed and adjusted during further development. In consequence, specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed and, whenever appropriate, adjusted to the current stage of development.

Analytical Procedures

The analytical methods should be described for all tests included in the specification (e.g. dissolution test method). For complex or innovative pharmaceutical forms, a higher level of detail may be required.

Validation of Analytical Procedures

The requirements for validation of analytical procedures for the IMP very much reflect the requirements for the active substance. Thus, for phase I clinical trials, the suitability of the analytical methods used should be confirmed. *The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form*, i.e. a validation scheme needs to be submitted. For clinical phases II and III, the suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation studies should be provided (e.g. results or values found) Again, there is no need to provide a full validation report.

Characterisation of Impurities

This section focuses on additional impurities/degradants observed in the IMP, which are not by-products of the synthesis (unless they are also degradation products).

Justification of Specification(s)

For IMPs in phase I clinical trials, it will be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the drug product. Toxicological justification should be given, where appropriate. In phases II and III, the choice of specifications and acceptance criteria for parameters which may affect efficacy or safety should be briefly justified.

Container Closure System

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated. Again, whenever possible, reference should be made to the relevant pharmacopoeial monograph. *If the product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided. For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions), more details may be needed.* It should be noted that for dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may be sufficient.

Stability

The shelf-life of the IMP should be defined based on the stability profile of the active substance and the available data on the IMP. Extrapolation may be used, provided that stability studies are conducted in parallel to the clinical studies and throughout their entire duration. The information presented should include the proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing study. *A stability commitment should be provided. Furthermore, bracketing and matrixing designs of appropriate IMPs may be acceptable, where justified.* However, it is of vital importance for the sponsor that the batches of drug product meet specification requirements throughout their entire period of use. *If issues arise, then the Competent Authorities should be informed of the situation, including any corrective action proposed.*

For phase I clinical trials, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under accelerated and long-term storage conditions will have been initiated. Whenever available, the results from these studies should be summarised in a tabulated form. *Supportive data from development studies should be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the clinical study should be provided.*

For phases II and III, the available stability data should be presented in a tabulated form. *An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the clinical study should be provided. Data should include results from studies under accelerated and long-term storage conditions.*

II. SPECIFIC SITUATIONS
IMPD for Authorised Test and Comparator Products in Clinical Trials

In addition to the simplifaction for test and comparator products authorized in the EU/EEA (see section "Simplified IMPD" in the EU-Commission document ENTR/CT1, included in Volume 10 of EudraLex), the guidelines foresees similar measures for test and comparator products authorized in the ICH -regions or in one of the Mutual Recognition Agreement (MRA)-partner countries, i.e. presently USA, Canada, Japan, Switzerland, Australia, New Zealand. However, in order to allow for future flexibility should further MRAs be signed, the guideline itself does not provide a list of these countries, but merely summarises them as described above. For products authorized in these countries, it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA as long as the product will not be changed in any way, including repackaging.

In addition, for products sourced from these non-EU/EEA countries, information on the analytical methods needed for at least reduced testing (e.g. identity) should be provided. *The relevant analyses, tests or checks necessary to confirm quality as required by Article 13 3(c) of directive 2001/20/EC shall therefore be based on proof of existence of the equivalent of a marketing authorisation, combined with confirmation of identity. As regards shelf-life, it will be sufficient to state the respective expiry date assigned by the manufacturer to the batch of product to be used in the study.*

For IMPs sourced from any other country (i.e. countries outside the EU/EEA, ICH regions and MRA-partner countries), a full documentation, according to the requirements stated in the general chapter of the guideline, should be submitted. Thus, the guideline allows for utmost flexibility in using test and comparator products authorized in the EU/EEA, ICH regions or MRA-partner countries. This should facilitate the conduct of studies not only aimed at EU licensing activities and help to keep the EU an attractive place for conducting clinical studies. In the light of the flexibility and simplification offered by this procedure, careful selection of the test and/or comparator product may save a lot of resources and can help to speed up the compilation and authorization of the IMPD.

Modified Authorised Test and Comparator Products in Clinical Trials

For the use in blinded studies, authorized comparator products are often modified or processed to various degrees. As the MAH of a comparator product is only responsible for the quality of the unchanged product in its designated and authorised packaging, any negative impact of modifications to the product performed by the applicant or sponsor of the clinical trial has to be outruled, with special emphasis on the biopharmaceutical properties. Accordingly, the IMPD for such a modified authorized product should be based on proof of existence of a marketing authorization (see section above) and the description of any modification performed. The level of detail will very much depend on the degree of modification.

Description and Composition

In the case of any modification of the authorised product other than repackaging, the complete quantitative composition of the preparation should be specified. All additional substances/materials added to the authorised product should be listed with reference to pharmacopoeial or in-house monographs. Whenever possible, only those excipients already present in the authorized formulation should be used to avoid potential incompatibilities. *For the authorised product itself, reference to the name and marketing authorisation (MA) number will suffice, including a copy of the SPC/PIL in Module 1.*

Pharmaceutical Development

The modifications carried out on the authorised comparator product should be described and any influence on the quality of the product needs to be discussed. Special focus should be laid on all parameters relevant for the function, stability and efficacy of the medicinal product, such as in vitro-dissolution and pH-value. *It should be demonstrated that these parameters remain comparable to those of the unmodified product. In case of solid oral dosage forms, comparative dissolution profiles of both original and modified comparator product should be provided to ensure unchanged bio-pharmaceutical properties.* It should be noted that in those cases where comparability cannot be established in vitro, additional clinical data to support equivalence may be necessary.

Batch Formula

The batch formula for the batch intended to be used during the clinical trial should be presented. However, this does not apply to authorised products which are only re-packaged.

Description of Manufacturing Process and Process Controls

All steps of the modification of the authorised medicinal product should be described, including in-process controls that are carried out.

Control of the Modified Comparator Product

Specifications

As for any IMP, release and shelf-life specifications should be submitted, including test methods and acceptance criteria. *Generally, they should include description and identification of the drug substance as well as the control of important pharmaceutical and technological properties, such as dissolution.* If the authorized product is a solid oral dosage form which is easily identifiable by its colour, shape and marking and the modification only pertains to encapsulating the intact dosage form, identification of the active substance may not be necessary, and visual examination may suffice for identification. Any further information to be provided will very much depend on the degree of modification of the authorised product. In certain situations, it may be necessary to specify and test additional quality criteria, e.g. determination of the drug substance(s) and impurities/degradants. However, as such a degree of detail will require the applicant/sponsor to perform an extensive analytical development, the most simple way of modification of the authorized product should be selected.

Analytical Procedures/Validation

For those parameters prone to be influenced by the modification and relevant to the performance of the comparator product, e.g. dissolution, the methods should be described. *The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.*

Characterisation of Impurities

In those cases, where the comparator product has undergone significant modification by the sponsor, e.g. has been processed with an excipient hitherto not present in the formulation with a likely impact on product stability, and the original product is not known to be stable under normal conditions, special emphasis should be given to demonstrating that the impurity profile has not changed compared to the original product. For stable comparator products, where a small degree of modification has been undertaken by the sponsor, e.g. where an intact tablet is encapsulated using the ingredients already present in the tablet, justification for not quantifying impurities will suffice (for definition of "stable" cf. Note for Guidance on Stability Testing of New Drug Substances

and Products (CPMP/QWP/2736/99), section 2.2.7 "Storage conditions"). This is not required for authorised products which are only re-packaged. As characterization of impurities will require significant analytical development work, consideration should be given to finding the most simple way of modifying the authorized product. For example, use of the double-dummy technique may present a suitable alternative to developing analytical procedures to characterize impurities.

Justification of Specification(s)

A justification of specification(s) will only be required in cases where a significant modification of the authorised comparator product may affect the product's performance or safety.

Stability

The applicant or sponsor of the clinical trial has to ensure that the modified comparator product is stable for at least the anticipated duration of the clinical trial in which it will be used. In the case of a significant modification, e.g. grinding of a tablet, re-lubrication and compression, or processing with an excipient hitherto not present in the formulation with a likely impact on product stability, a minimum of stability data on the modified comparator product should be available, depending on the length of the planned clinical trial, prior to the start of the clinical trial in order to allow an assessment of the impact of the modifications on product safety and stability. The available stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the clinical study should be provided. Any degree of extrapolation may not exceed the shelf-life originally assigned to the specific batch of authorised product by its MAH.
In the case of only minor modifications, a justification of the stability over the intended study period may be acceptable.

Test Products Containing Existing Active Substances in Bio-Equivalence Studies, e.g. Generics

Whereas the first section of the guideline focusses on those IMPs that either contain a new active substance or are used in a complete clinical development program, the section on test products containing existing active substances in bio-equivalence studies mainly focusses on the "bio-batch" to be used to establish bioequivalence of a generic to the reference product. In many cases, the active substance will not only be a well-known one, but it will also be covered by a monograph in the pharmacopoeia. Also, as the bio-equivalence study for a generic will be conducted at an overall stage in development more comparable to phase III than phase I of a complete clinical development, certain

requirements, e.g. on validation of analytical methods, reflect the requirements for phase II/III in the general requirements section.

In the following, only those sections of the IMPD of a test product containing existing active substances in bio-equivalence studies will be high-lighted that differ from the general requirements described in the first section.

Active Substance

Description of Manufacturing Process and Process Controls

For substances which comply with a monograph of the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required. It is, however, important to note the need to demonstrate the suitability of the monograph to adequately control the quality of the active substance. This can be done – as described in the general section – by a CEP, using the ASMF-procedure or by providing the respective information in the IMPD itself. *In cases where reference to a pharmacopoeial monograph listed above cannot be made or compliance has not been demonstrated, a brief summary of the synthesis process, a flow chart of the successive steps including, for each step, the starting materials, intermediates, solvents, catalysts and reagents used should be provided. The stereo-chemical properties of starting materials should be discussed, where applicable.*

Specifications

The microbiological quality of drug substances used in aseptically manufactured products should be specified.
For substances which comply with a monograph of the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvents and catalysts as they are not included in the pharmacopoeial specification.
In cases where reference to a pharmacopoeial monograph listed above cannot be made, specifications, tests used as well as the acceptance criteria should be provided for the batch(es) of the drug substance(s) intended for use in the bio-equivalence study.

Analytical Procedures and Validation

For substances for which reference to a pharmacopoeial monograph listed above cannot be made, the analytical methods used for the drug substance (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC, etc.) should be provided. *It is not necessary to provide a detailed description of the analytical procedures.* Basically, these requirements are identical to the ones described in the general section. However, as described above, the requirements regarding

validation of analytical procedures reflect the requirements for phase II/III for new active substances.

For substances for which reference to a pharmacopoeial monograph listed above cannot be made, the suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods should be provided (e.g. values found for repeatability, limit of quantification etc.). It is not necessary to provide a full validation report.

Stability

The requirements on stability data for an existing active substance again somewhat differ from the ones for a new active substance as much more information will be available at the time a bio-equivalence is going to be conducted compared to a phase I study with a new active substance. Though not necessarily predictive for the stability of an IMP, information on the stability of the active substance will facilitate understanding the stability profile of the IMP itself and is valuable information to support the proposed shelf-life of the IMP which – as described below – can be based on limited information. *The available stability data of the active substance should be provided in a tabulated form. Alternatively, confirmation that the active substance will meet specifications at time of use will be acceptable.*

Investigational Medicinal Product under Test

Description of Manufacturing Process and Process Controls

As the bio-equivalence study will be conducted with an IMP representative for the future market product, the focus here is really on the specific formulation and manufacturing process to be used for the manufacture of the bio-batch. Therefore, in contrast to the requirements in the general section, there is no need to compare formulation or manufacturing process to IMPs used in previous clinical studies. *A flow chart of the successive steps, including the components used for each step and including any relevant in process controls, should be provided. In addition, a brief narrative description of the manufacturing process should be included.*

Specifications

As regards specifications for the IMP, it will be sufficient to provide the chosen release and shelf-life specifications, including test methods and acceptance criteria.

Analytical Procedures and Validation

The analytical methods should be described for all tests included in the specification with a special focus on tests that are relevant for the performance

of the IMP (e.g. dissolution test method). *For complex or innovative pharmaceutical forms, a higher level of detail may be required.*

Same as for the active substance, expectations regarding validation information are comparable to the ones described for phase II/III for IMPs in a complete clinical development program. Thus, the suitability of the analytical methods used should be demonstrated. *A tabulated summary of the validation results should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate).* Again, it is important to note that at no point in time it is necessary to provide a full validation report.

Stability

Stability information for IMPs containing existing active substances and intended for bioequivalence studies somewhat differs from the requirements described in the general section. Bio-equivalence studies will be performed on a rather limited number of volunteers, they will normally only need a short period of time and the IMP to be used will normally be identical to the product to be marketed. As described for IMPs containing new active substances, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) of the IMP and that, prior to the start of the clinical trial, at least studies under accelerated and long-term storage conditions will have been initiated. In addition, the results from at least one month accelerated studies or the results of the initial phase of studies under long-term storage conditions should be summarised in a tabulated form. Supporting data from development studies will definitely be helpful to convince competent authorities of the adequateness of the proposed shelf-life and should therefore also be submitted (summarised in a tabular overview). *An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the bio-equivalence study should be provided. Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study.* For extrapolation and the possibility to use reduced stability testing designs, i.e. bracketing and matrixing, see information provided in the general section.

Placebo Products in Clinical Trials

Following a request from industry, the final version of the guideline also contains a section on quality requirements for placebo products to be used in clinical trials. Given the nature of placebos, this section focuses on the information on the IMP itself.

Description/Composition and Pharmaceutical Development

The qualitative and quantitative composition of the placebo should be stated. A short statement or a tabulation of the dosage form and the function of each

excipient should be included. As regards the development of the placebo formulation, a description is required how possible differences of the placebo preparation in relation to the investigational medicinal product regarding taste, appearance and smell are masked, where relevant.

Manufacturing Process/Process Controls and Control of Critical Steps and Intermediates

A flow chart of the successive steps, indicating the components used for each step and including in-process controls should be provided. In addition, a brief narrative description of the manufacturing process should be included. Information on the control of critical steps and intermediatesis only requested in case of manufacturing processes for sterile products.

Process Validation and/or Evaluation

As desribed in the general situation, data on process validation/evaluation are only required in specific risk-relevant situations, e.g. non-standard sterilisation processes not described in the Ph. Eur., USP or JP. In these cases, the critical manufacturing steps, the validation of the manufacturing process and the in process controls need to be described in the IMPD.

Specifications

In line with requirements for IMPs containing active substances, the chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. *The specifications should at minimum include a test which enables to clearly differentiate between the respective investigational medicinal product and the placebo.*

Stability

The shelf life of the placebo product should preferably cover the anticipated duration of the clinical trial. However, stability studies on placebo products are only required in specific situations, e.g. those cases where there is reason to suspect that the placebo product will undergo changes in its physical characteristics such as hardness or appearance, allowing for an easy distinction between placebo and IMP. In all other cases, a short justification of the assigned shelf-life will be sufficient.

Appendices

The guideline also contains several appendices, describing specific requirements which may be of relevance for any kind of IMP, including placebos.

Adventitious Agents Safety Evaluation

Due to their inherent risk, all materials of human or animal origin used in the manufacturing process of both drug substance and drug product, or such materials coming into contact with drug substance or drug product during the manufacturing process, should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin has to be provided in a separate appendix to the IMPD.

TSE AGENTS

Detailed information should be provided on the avoidance and control of transmissible spongiform encephalopathy agents. This information can include, for example, certification and control of the production process, as appropriate for the material, process and agent.
The "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01" in its current version is to be applied.

VIRAL SAFETY

Whenever applicable, i*nformation assessing the risk with respect to potential viral contamination should be provided. The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should be evaluated.*

OTHER ADVENTITIOUS AGENTS

Detailed information regarding the other adventitious agents, such as bacteria, mycoplasma, and fungi should be provided in appropriate sections within the core dossier wherever relevant.

Novel Excipients

For novel excipients, information identical to the information required for a new active substance has to be provided, consistent with the respective clinical phase. Thus, the same staged-approach applies to the information required for novel excipients as for new active substances.

Changes to the Investigational Medicinal Product with a Need to Request a Substantial Amendment to the IMPD

In addition to the need for an IMPD to be filed with the application, Good Manufacturing Practices require that a Product Specification File (PSF) has to be maintained for each IMP at the respective site. This PSF needs to be continually

updated as the development of the product proceeds, thus always reflecting the latest developments. In addition, appropriate traceability to the previous versions of the PSF needs to be ensured.

For various reasons, there may also arise the need for changes regarding the information requested and provided in the IMPD during an ongoing study. The guideline contains a final section that provides information on situations where and when changes need to be notified to the competent authorities.

For information provided on the quality of an IMP in the dossier, the guideline and the underlying guidance document of the Commission list the following examples of changes to IMP quality data concerning

- Importation of the medicinal product
- Change of name or code of IMPs
- Immediate packaging material
- Manufacturer(s) of drug substance
- Manufacturing process of the drug substance
- Specifications of active substance
- Manufacture of the medicinal product
- Specification (release or shelf-life) of the medicinal product
- Specification of excipients where these may affect product performance
- Shelf-life including after first opening and reconstitution
- Major change to the formulation
- Storage conditions
- Test procedures of active substance
- Test procedures of the medicinal product
- Test procedures of non-pharmacopoeial excipients

as only to be regarded as "substantial" where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the patients;
- the scientific values of the trial;
- the conduct or management of the trial;
- the quality or safety of any IMP used in the trial.

It is important for the applicant/sponsor to be aware that in all cases, an amendment is only to be regarded as "substantial" when one or more of the above criteria are met. The quoted list is not exhaustive; a substantial amendment might occur in other aspects of a clinical trial as described in the 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" in its current version.

Assessment of an IMPD should be focussed on patient safety. Therefore, any amendment involving a potential new risk has to be considered a substantial amendment. This may be especially relevant for changes in impurities, microbial

contamination, viral safety, TSE and in some particular cases to stability when toxic degradation products may be generated. However, the applicant/sponsor should be aware that first and foremost it is his own responsibility to perform an adequate risk assessment of the implications of any change. As stated above, only those changes need to be notified in a substantial amendment that are likely to have a significant impact on the safety or physical or mental integrity of the patients, on the scientific values of the trial, on the conduct of management of the trial or on the quality of safety of any IMP used in the trial (with the latter condition being most relevant for quality changes).

The amendments refer to the submitted IMPD. Should the changes be covered by the IMPD as submitted, a notification of a substantial amendment will not be necessary. Also, *when an amendment will become effective with the start of a new clinical trial (e.g. change of name of the IMP, new manufacturing process), the notification will take place with the application for the new trial. Notifications of substantial amendments are only necessary for changes in ongoing clinical trials.* Therefore, in order to minimize any potential risk of a disruption of or delay in an ongoing clinical trial, the sponsor should carefully check whether the specific change needs to be performed during a study and cannot be postponed until the next study will be initiated.

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 CardioSec Clinical Research GmbH Peterstrasse 5, 99084 Erfurt, Phone +49(0)361-789 197 40 Fax ..44, e-mail: info@cardiosec.com, web: www.cardiosec.com

About the authors

Susanne Keitel is a licensed pharmacist and holds a PhD. in pharmaceutical technology. With professional experience of 10 years as a scientist and department head in the pharmaceutical development industry, she joined the Federal Institute for Drugs and Medical Devices (BfArM) as division head Pharmaceutical Quality in 1997. Since 2005, Susanne Keitel is Head of EU, International Affairs at BfArM. She is vice-chair of the Joint CHMP/DVMP Quality Working Party and EU representative in the ICH process where she has been rapporteur and topic leader for the stability guidelines and ICH Q8 "Pharmaceutical Development".

Hans-Joachim Janhsen, PhD, a licensed pharmacist, has over 22 years experience in various senior management positions in the pharmaceutical industry. These have focused on operations and general management, including extensive experience in handling GxP topics in the international environment, especially North America.

Hans-Joachim Janhsen provides consultancy service to the pharmaceutical industry and is managing partner of CardioSec Clinical Research GmbH www.cardiosec.com

For correspondence:

Dr. Hans-Joachim Janhsen c/o
CardioSec Clinical Research GmbH
Peterstr. 5
99084 Erfurt
Germany

Phone +49(0)361-789 197 40

Fax +49(0)361-789 197 44

e-mail: hansjoachim.janhsen@cardiosec.de

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CardioSec Clinical Research GmbH http://www.cardiosec.com
Dr. Hans-Joachim Janhsen
Peterstr. 5
99084 Erfurt
Germany

Phone +49(0)361-789 197 40
Fax +49(0)361-789 197 44
e-mail: hansjoachim.janhsen@cardiosec.de

Representatives:
USA:

Pharmaceutical Regulatory Services, Inc.
Jurij Petrin, M.D.
58 Fairway Drive
Princeton, NJ 08540 USA

Phone +1 (609) 497-9694
Fax +1 (609) 497-9695

e-mail: jurij.petrin@pharmregservices.com

Switzerland:

PFC Pharma Focus AG
Chriesbaumstrasse 2
8604 Volketswil, Switzerland
Phone +41-(0)44-908 6666
Fax +41-(0)44-908 6677

e-mail kurt.pfister@pfc-cro.com