European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

**Division Certification of Substances**

CP/CB

**PUBLIC DOCUMENT**
(Level 1)

*English only/Anglais seulement*

**PA/PH/ CEP (04) 1 4R**

February 2007

**Certification of suitability of Monographs of the European Pharmacopoeia**

# Content of the dossier for chemical purity and microbiological quality

(Revision of Annex I Resolution AP-CSP (93) 5 as amended)

| | |
|---|---|
| Submission to Technical Advisory Board (Chemical) | January 2007 |
| Revision following discussion in TAB and comments received | February 2007 |
| Submission to the Steering Committee members | March 2007 |
| Adopted by the Steering Committee members | March 2007 |
| Implementation | May 2007 |

Strasbourg

Address: 7 allée kastner CS 30026 - F 67081 Strasbourg
Telephone: 33 (0) 3 88 41 30 30 - E-mail: certification@edqm.eu - Fax: 33 (0) 3 88 41 27 71
Internet : http://www.edqm.eu

# CONTENT OF THE DOSSIER FOR A SUBSTANCE FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY EVALUATION

The Application Form – Request for New Certificate of Suitability together with the relevant annexes should be completed (available for download from the EDQM web-site (http://www.edqm.eu).

Dossiers should be presented according to the CTD format (see The Rules Governing Medicinal Products in the European Community – Notice to Applicants for marketing authorizations for medicinal products for human use in the member states of the European Community, Volume 2B) as presented below except when justified.

References to guidelines are inserted to assist applicants. It remains the applicant's responsibility to ensure that all relevant legislation and guidelines, as revised or maintained, are respected in the application when applicable. The guidelines referenced in each section provide useful information on the content expected in that section. However, this list should not be regarded as comprehensive. The requirements of the general monographs *Substances for Pharmaceutical Use* (2034), *Products of Fermentation* (1468) and *Products with risk of transmitting agents of animal spongiform encephalopathies* (1483) should be respected in the application, when applicable.

The applicant should also provide the Certification Secretariat of the EDQM with samples of 1 or 2 representative commercial batches in sufficient quantity to perform a complete analysis (normally about 10 g). Where applicable, samples of impurities are required where revision of the monograph is requested and/or if an additional method(s) to limit the related substances is (are) appended to the certificate for possible checking by the laboratory of the EDQM.

## Information about the Expert (1.4)

The Expert's c.v. showing his/her experience in the concerned field should be given.

## Quality Overall Summary (QOS) (2.3)

A summary of the content of the dossier should be given in the form of a Quality Overall Summary (QOS)-(see The Rules Governing Medicinal Products in the European Community – Notice to Applicants for marketing authorizations for medicinal products for human use in the member states of the European Community, Volume 2B). It is expected that the Quality Overall Summary (QOS) should discuss the ability of the European Pharmacopoeia monograph to control the quality of the active substance, and in particular the declared potential impurities, or the necessity for alternative methods. Particular attention should be given to justifying cases where testing for possible impurities is omitted, for example due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production. The report should be signed and dated.

General information (3.2.S.1)

Commercialisation history of the substance:

Summarise the licensing history for medicinal products licensed in Europe that contain the substance made by the defined method of manufacture naming the countries, products and commercialisation dates. It should be made clear whether the products are for veterinary use. Information on the Active Substance Master Files submitted to the National Licensing authorities should be supplied. This information should be given in the relevant sections of the administrative form.

Declarations:

A signed declaration from the manufacturer that manufacture is conducted in accordance with the presented dossier and with a specified guideline on GMP should be supplied, preferably with the administrative form. The applied GMP should comply with *Vol. 4 of the Rules Governing Medicinal Products in EU* and apply for each manufacturing step from the introduction of the starting materials (see Control of materials 3.2.S.2.3). If available a copy of a GMP certificate should be supplied. Other approaches to GMP of similar standards are acceptable, if justified.

A signed declaration that the manufacturer is willing to be inspected, in accordance with the relevant legislation, on the request of a relevant authority before and/or after being granted a certificate of suitability should be supplied. When the proposed holder is not the manufacturer this declaration should also be provided by the proposed holder together with a declaration from the active substance manufacturer committing them to keep the proposed holder informed of any changes to the documentation so that this may be declared to the EDQM.

Other parties may be mentioned on the certificate where relevant. If other parties are involved in certain stages of the process, details of their involvement and of other site addresses must be provided and information given on the contractual arrangements regarding sole or shared responsibilities. If an additional site is to provide alternative capacity batch analysis results for impurity profiles must be provided to demonstrate that the alternative arrangements yield product of the same quality as that produced by the first site.

When the manufacturer of the final substance performs only the purification of a crude substance supplied by a contract manufacturer that is a not a subsidiary of the manufacturer of the final substance separate declarations on GMP and willingness to be inspected should be provided for the contract manufacturer(s). This could also be the case for any other contract manufacturer that is not a subsidiary including laboratories.

A declaration on the use/non-use of material of animal or human origin during manufacture should be supplied. Where materials of animal or human origin are used in the process, this will be mentioned on the certificate. In this case, CEP holders and MA holders should be aware that viral safety data are to be submitted in the MA dossier. If material of animal origin which may be susceptible to TSE contamination is used, compliance with the European Pharmacopoeia monograph *Products with risk of transmitting agents of animal spongiform encephalopathies* (1483) should be demonstrated as described in the document *Content of the dossier for a substance for TSE risk assessment* (PA/PH/CEP (06) 2).

Nomenclature (3.2.S.1.1):

The European Pharmacopoeia monograph name, the INN, and other chemical name(s) should be stated together with any laboratory code used in the dossier.

General properties (3.2.S.1.3):

In case more than one grade, in respect of physical characteristics, is produced, the manufacturer may wish to submit one or more dossiers depending on whether or not separate certificates are applied for. Examples are: compacted, special particle size, particular polymorphic form (where the monograph does not restrict to one single polymorph). In any case the different qualities shall comply with the general level of quality defined in the monograph. If more than one grade is described in the same dossier (i.e. only one certificate is asked for) the batch analysis results, in respect of impurity profiles, should include all grades. It is optional to mention the different grades in the sub-title of the certificate (this should be made clear on the administrative form). However, the possibility for one certificate to cover different grades cannot be applicable when these different grades require different specifications and/or methods for the control of impurities; in which case separate certificates will be needed and the relevant grades will be mentioned in the sub-title of the certificate. For grades not described in the European Pharmacopoeia the specifications describing the determination of the physical grade should be given with the used analytical method as well as the characterisation of the physical properties.

In other cases the manufacturer may want to present individual dossiers for each grade with a view to obtaining separate certificates for each grade, which will also be mentioned in the sub-title of the certificate (this should be made clear on the administrative form).

It should be noted that:

- As explained in the general monograph *Substances for Pharmaceutical Use* (2034) mixtures that are manufactured from defined active substances or excipients are only acceptable if this is specifically stated in the definition of the individual monograph. Suitable test methods and limits for any additives should be provided.

- Acceptable claims regarding sterility/freedom from pyrogens and/or bacterial endotoxins should be indicated and reference given to the relevant test of the monograph (sterility/LAL/pyrogens) and the method used for sterilisation should be identified and which will be stated on the certificate. The document *Certificates of suitability for sterile active substances* (PA/PH/CEP/T0(6) 13,1R) should be taken into consideration. It is only possible to introduce grades for freedom from pyrogens and/or bacterial endotoxins on the CEP when the monograph foresees this. Separate files will be needed if both grades are produced (non-sterile and sterile, apyrogenic/bacterial endotoxin-free and non-apyrogenic/endotoxin free substances).

In the particular case where the monograph covers different grades of the substance (i.e. lactulose liquid or sodium lactate solution, various per cent concentrations of dimeticone, viscosity) it is possible to mention different grades in the sub-title of the CEP if the concentrations/viscosity etc are within the range of the monograph and also if the monograph states that the label should mention the particular grade.

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1):

If different sites/facilities are involved for a single defined process for manufacture and/or testing this should be explained and it should be made clear which production step is conducted on which site and the names and addresses of each of them should be given.

Description of manufacturing process and Process Controls (3.2.S.2.2):

Applicants are reminded that the requirements of the general monographs *Products of Fermentation* (1468) and *Products with risk of transmitting agents of animal spongiform encephalopathies* (1483) should be respected when applicable.

The following information should be supplied:

— An outline (flow chart, including the structural formula for the starting materials and all intermediates),

— The description of the manufacturing method should include all the steps of the process, proceeding from the starting materials(s) to any isolated intermediates, and ultimately to the active substance.

— Detailed description of each stage of the manufacture, including information on solvents and reagents, catalysts, conditions of reactions, information on intermediates, which are isolated and purified, quantities of all materials used in the process to produce a batch of the typical commercial size and yields for isolated intermediates should be indicated for each process step. Special emphasis should be given to the final steps including purification procedures.

— The maximum batch size for which the manufacturer has acquired experience with the defined method, and which should correspond to batches referred to in the dossier, should be stated. Where the substance has yet to be produced in commercial quantities (only pilot scale batches manufactured) the certificate can be granted provided scale-up is immediately reported to the EDQM. For a sterile product, an application for a variable and/or alternative batch size should be justified.

— In case of semi-synthetically manufactured substances the fermented starting material should be well characterised, and the possibility of carrying impurities from the fermentation process to the final substance should be discussed. Each supplier should give a declaration on the use/non-use of material of animal origin during manufacture of the starting material. Note that products obtained only by purification or salification of a fermented starting material cannot be considered as semi-synthetic products and should therefore be subject to the same requirements as true products of fermentation.

— Different manufacturing sites and different manufacturing methods or alternatives could be described in a single dossier provided that proof is given that for each case the specifications

and the impurities profiles are exactly the same. If more than one manufacturer/facility is involved in manufacture, the responsibilities of each party should be clearly indicated.

— Whatever type of manufacturing process is used, alternatives are not allowed unless they are clearly defined and detailed as part of 2nd, 3rd etc. processes. Batch analysis results corresponding to the substance manufactured according to the different alternatives must be provided to demonstrate that there are no significant differences in impurity profiles, which may affect the specifications. If this provision is not met, the application will need revision to delete one or more of the options, which results in a product that does not conform to the 'standard' profile. ‘Deleted’ options may be included in further applications for additional certificates.

If re-processing (i.e. re-application of a step already described in the process) is a possibility it should be mentioned and should be treated as a procedural option.

Normally re-working (application of steps different from those of the process) is not acceptable since this implies the use of different solvents, which leads to a change in the specifications, and /or impurity profile of the substance. A separate certificate application would therefore be necessary to cover material produced using such a procedure.

Recovery (e.g. from mother liquors or filtrates) of reactants, intermediates or the final substance is considered acceptable provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use. The specifications should be described. However, recovery of the substance without any further purification of the obtained substance according to the usual process should be considered as a re-working and is not acceptable.

Blending of production batches of the final substance to obtain a larger size is acceptable provided each batch incorporated into the blend is individually tested and found to meet specifications set for the final substance prior to blending.

Control of materials (3.2.S.2.3):

Appropriate specifications for raw materials and solvents should be supplied. If materials are recycled then justified specifications for the recycled materials should be supplied and it should be made clear in which manufacturing step they are used. When a class 1 solvent could be present in a solvent used during manufacture e.g. benzene in toluene a suitable limit and analytical method for its control should be introduced.

Applicants should propose and justify which substance(s) should be considered as the starting material(s). They should be fully characterised and complete specifications should be provided including an impurities profile. The possibility that impurities present in the starting material may be carried through the process unchanged or as derivatives should be discussed and if relevant be controlled in starting material by appropriate acceptance criteria. A description of analytical controls applied to ensure the quality of the starting materials should be given. Relevant viral safety and/or TSE data should be provided if any animal derived material is used during the manufacturing process. Starting materials from vegetable origin should be fully characterised to ascertain suitability, and a contaminant profile should be established and submitted.

In the case of a route of synthesis consisting of one or only a few steps, full details of the manufacture of the starting material(s) should be given and/or at least detailed specifications especially regarding the impurity profile including residual solvents and catalysts. Alternatively, for starting materials described in the European Pharmacopoeia certificates of suitability can be provided, if available.

The supplier(s) of the starting materials(s) should be declared and where more than one supplier is used batch analysis results from the substance manufactured from the different suppliers should be given.

Controls of critical steps and intermediates (3.2.S.2.4);

Any critical steps should be identified. Tests and acceptance criteria performed at the critical steps should be provided. In-process controls should be described. Information on the quality and control of intermediates isolated during manufacture should be provided.

Process validation and/or evaluation (3.2.S.2.5);

Process validation and/or evaluation studies shall be provided as appropriate. In particular, sterilisation processes including filtration and aseptic processing should be validated. Therefore, when a request to mention sterile in the sub-title of the certificate is made validation data should be presented in the dossier. European Pharmacopoeia General text 5.1 should be taken into consideration. In addition, a full description of the sterilisation process is required, including for sterilisation by filtration, the maximum acceptable bio-burden prior to the sterilisation, the type of microbial retentive filter used and its pore size (pore sizes of 0.22 μm or less are acceptable without further justification), any in-process controls (i.e. filter integrity) as well as the method(s) of sterilisation of the primary packaging material. CEP holders and MA holders should be aware that when the active substance is used after sterilisation as a medicinal finished product e.g. sterile powder distributed in sterile packaging, the sterilisation of the active substance will be considered as an intrinsic part of the manufacturing process of the medicinal product. Consequently, full data must be provided in the application file for a medicinal product or by the licensing authority requesting the assessment report from the EDQM.

When the monograph indicates specific additional requirements for the manufacturing process (i.e. in the production section of the monograph) compliance to this aspect should be demonstrated when reference to a specific test(s) is given. For biological substances (such as heparin sodium), and even if a specific microbial grade is not requested to be mentioned on the certificate (sterile, endotoxin free, ..), the dossier should include information demonstrating suitable inactivation and/or removal of any infectious agent.

Elucidation of Structure and other Characteristics ((3.2.S.3.1)

Impurities (3.2.S.3.2)

Related substances:

The requirements of the related substances section of the general monograph *Substances for Pharmaceutical Use (2034)* and the guideline *Control of impurities of pharmacopoeial*

*substances* (CPMP/QWP/1529/04) should be met. It should be demonstrated that all applied methods are suitable to control impurities at the applicable levels set by the general monograph. Furthermore the provisions of the general chapter *Control of impurities in substances for pharmaceutical use (5.10)* are to be taken into consideration.

Possible impurities originating from the route of synthesis or from degradation should be listed and discussed with an indication of their origin (starting material, reagent, solvent, catalyst, intermediate, degradation product). The impurities that are controlled should be presented together with details of the analytical methods used, and a list of the related substances found in the substance. The related substances found in batches of the active substance should be compared with the related substances listed in the transparency statement of the monograph (where one exists) together with their typical levels and the proposed limits.

**The suitability of the method(s) of the monograph to control the quality of the substance must be discussed and demonstrated.** In particular, where additional impurities (i.e. those not listed in the transparency statement of the monograph) are found above the relevant reporting threshold and disregard limit of the monograph it must be demonstrated whether the monograph controls them and where applicable retention times or Rf values and limits of detection and/or quantification should be provided. If the monograph does not control the additional impurities, suitably validated sadditional test(s), should be proposed. Evidence should be given of the absence of impurities not routinely tested for in the product or its intermediates.

Chromatograms for production batches of the substance suitably zoomed and annotated and with peak area results should be supplied.

Where additional related substances are present (those not already mentioned in the monograph) they should be considered according to the related substances section in the general monograph *Substances for Pharmaceutical Use* (2034) (which corresponds to the requirements of the ICH note for guidance Impurities in New Drug Substances CPMP/ICH/2737/99). Suitable limits should be set which should be justified. In particular, where present above the relevant identification threshold they are identified and when present above the relevant qualification threshold they should be qualified. Alternatively, and where appropriate, it may be demonstrated by other means that the impurity profile (number, nature, amount) of the substance is comparable to that of products already on the market. For active substances excluded from the requirements on related substances of the general monograph *Substances for Pharmaceutical Use* (2034), and which contain additional impurities, qualified limits should be proposed and where necessary toxicological data should be supplied.

In the case of particularly toxic impurities, the determination of acceptable levels is a critical issue to be documented. The EMEA CHMP Guideline on the *Limits of Genotoxic Impurities* (EMEA/CHMP/QWP/251344/2006), effective as of 01 January 2007, is applicable to new applications for existing active substances in conditions described in the scope of the guideline. A specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential genotoxicity. If a genotoxic impurity is liable to be present in the substance then conformity to the requirements of the guideline should be demonstrated in the CEP application file.

In discussing possible degradation products, reference to data from real time stability studies or from stress testing or reference to the literature may be helpful. However, results from formal stability studies are not a requirement when there is no request to mention a retest period on the certificate.

If alternative routes of synthesis are described the possible impurities are discussed separately for each route.

Other impurities:

Residues of residual toxic reagents should also be discussed and where applicable a suitable limit and test method proposed if the monograph does not provide a suitable test.

Residues of acids or bases that are not mentioned in the ICH guideline for residual solvents (e.g. HCl, organic acids) should also be discussed if the monograph does not provide a suitable test (pH, acidity or alkalinity).

Concerning residual triethylamine, a permitted daily exposure (PDE) of 3.2 mg/day giving a limit of 320 ppm (for a 10 g daily dose) was calculated from repeated Dose Toxicity and Reproductive Toxicity data. This limit of 320 ppm should therefore be used as a reference limit. Higher limits should be justified by batch analysis data and the maximum daily dose of the concerned substance. It should be noted that this limit is not immediately applicable to other organic bases for which limits should be calculated on available toxicological data.

Residual solvents:

The European Pharmacopoeia general chapter 5.4 Residual Solvents is to be applied. In addition, the Annexes to: CPMP/ICH/283/95 Impurities: Guideline for Residual Solvents & CVMP/VICH/502/99 Guideline on Impurities: Residual Solvents *Annex I: Specifications for class 1 and class 2 residual solvents in active substances* (CPMP/QWP/450/03, EMEA/CVMP/511/03) should be taken into consideration when setting specifications.

As indicated in the general chapter class 1 solvents should not be employed in the manufacture of active substances or excipients unless there is a benefit/risk justification, which should be provided. The final decision on the acceptability of the use of a class 1 solvent during manufacture will be taken by the Technical Advisory Board.

If class 2 solvents are only used in a step of the manufacturing process prior to purification, the absence of such solvents in the final product should be demonstrated to justify the exemption of a test. Otherwise a suitable specification should be introduced. Toxic solvents (Class 1 and 2) should always be limited using a specific test, e.g. the test described in the general methods of the European Pharmacopoeia.

Any limit higher than the ICH option 1 limit should be justified according to an option 2 calculation, i.e. based on the daily dose (for class 2 solvents only).

Low toxic solvents (Class 3) can be limited by a test for Loss on drying with a limit of not more than 0.5%. For solvents used in previous steps and absent or at a low level their control may be omitted. If the limit in the loss on drying test of the monograph is more than 0.5%, or it is not possible to introduce a loss on drying test, a specific test for residual solvents should be introduced.

For solvents not listed in the general chapter or listed in table 4 of the general chapter and which need to be mentioned on the certificate toxicological justification of the proposed limits should be supplied.

Solvents to be controlled will be mentioned on the certificate with the relevant test(s) and limit(s) (except those mentioned in the specific monograph).

Residual catalysts:

Where catalysts are used in manufacture satisfactory information to demonstrate that there is no entrainment of metal catalysts should be supplied. If there is carry over a suitable and justified control limit should be proposed together with a validated method for determining the residual catalyst.

Control of Drug substance (3.2.S.4)

Specification (3.2.S.4.1):

The specifications should be in accordance with the current general and specific European Pharmacopoeia monographs. Where the monograph has been shown not suitable to control the quality of the substance, and in particular the related substances, the additional analytical methods should be identified. Any additional specifications to those of the monograph shall be justified.

Where the monograph includes a production section the requirements of this section should be respected in the application dossier.

European Pharmacopoeia monograph under revision:

If the monograph is in the process of being revised, the draft monograph will be taken into consideration during evaluation since the current monograph is viewed as insufficient and therefore the manufacturer may also wish to take it into consideration in the application dossier. However, application of the revised monograph is not mandatory before the implementation date.

Analytical procedures (3.2.S.4.2):

If specifications and test methods other than those described in the monograph concerned of the European Pharmacopoeia are used, they must be fully described and validated (see below). They would be appended to the certificate only if shown to be needed as supplementary to those of the monograph (which are shown insufficient). Monographs describing a TLC method to control related substances are generally not considered to comply with the requirements of the general monograph *Substances for Pharmaceutical Use* (2034) and general chapter 5.10 *Control of impurities in substances for pharmaceutical use* and therefore a quantitative method should be proposed by applicants to control the related substances liable to be present in the substance. This method would then be appended to the CEP. The TLC method would be accepted in rare cases only i.e. as only rarely are the requirements of the general monograph on *Substances for Pharmaceutical Use* and the general chapter 5.10 *Control of impurities in substances for pharmaceutical use* satisfied by a TLC method. It would also be acceptable in cases where a particular related substance is controlled by a TLC method but a quantitative method is also described in the monograph to control related substances.

To facilitate the preparation of the certificate a separate description of any supplementary tests should be presented.

Validation of analytical procedures (3.2.S.4.3):

If purity testing methods other than or supplementary to those of the European Pharmacopoeia are used the analytical validation should be supplied. Where the official method of control of related substances is used, and it is declared that only those related substances listed in the transparency statement of the monograph are present in their substance, it should be demonstrated that no other impurities are detected. Typical chromatograms should be presented together with the characterisation of the reference substance(s). Where additional or alternative methods are used in quality control of the final substance they should be adequately validated and/or cross validated with reference to the monograph's method(s) using Ph. Eur. CRS where prescribed. Where appropriate typical chromatograms should be available.

If an additional method is exactly as described in the general methods of the European Pharmacopoeia (i.e. general method 2.4.24 for residual solvents) a full validation is not required but the method should be described and only applicability to the concerned substance should be demonstrated. For the determination of residual solvents the method of sample preparation and the used system (A or B) should be specified. Methods from a specific monograph of another Pharmacopoeia do not have to be fully validated (though specificity and level of detection and/or quantification should be calculated). If the method of the specific monograph is used to control additional impurities a minimum validation should be done (specificity and limits of detection and quantification).

Batch analyses (3.2.S.4.4):

To be able to re-evaluate the monograph of the European Pharmacopoeia the results of a full testing of at least two batches will be given. Results below 1.0 % for related substances should be reported with two decimal places e.g. 0.25 %. When different grades, methods of manufacture or alternatives or different sites are described in the dossier, the results of the analysis of the batches shall be provided for each of them. The batch size, and the date of manufacture and analysis will be given. The results of the analysis are given as actual figures whenever possible instead of statements such as “conforms”, “complies” etc

The batch size should be in accordance with the declared maximum batch size as specified in the description of the manufacturing process.

The results submitted should be discussed in relation to the limits of the European Pharmacopoeia monograph and possible supplementary tests.

Justification of specification (3.2.S.4.5)

It should be stated if supplementary or improved tests are needed. Any additional specifications or deviations should be justified. The possible need for a revision of the European Pharmacopoeia monograph should be discussed.

Omission of tests:

Where the monograph mentions a test for a named impurity (metal catalyst/reagent/solvent) but which is not used during manufacture, the manufacturer may omit the test in the specifications which should be made clear in the dossier. If the proposal of the applicant is accepted, a clear statement on this subject will be reported on the CEP. However, the substance should comply with the monograph, if tested.

Reference standards or materials (3.2.S.5)

When in-house standards/working standards, non-official or official standards other than the appropriate Ph. Eur. CRS are employed, they have to be suitably described (in terms of identification, purity, assay, etc) and their establishment has to be demonstrated. If other standards are used instead of their respective Ph. Eur. CRS an appropriate comparison to the Ph. Eur. CRS is required.

Container closure system (3.2.S.6)

The container closure–system should be described and the specifications (including description and identification) should be supplied. Where relevant conformity to the note for guidance *Plastic Primary Packaging Materials* (CPMP/QWP/4359/03) should be shown. The compatibility with the requirements of the storage section of the specific monograph (e.g. for airtight containers) should be demonstrated.

Stability (3.2.S.7)

As stated in the note for guidance *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02) for substances described in an official Pharmacopoeia monograph which covers the degradation products, results from formal stability studies are not necessarily required. However, when a retest period is requested to be mentioned on the certificate (which should be made clear on the administrative form) it should be determined in accordance with *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02 Rev 1) and the Annex: *Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances* (CPMP/QWP/609/96 Rev. 1)). Results from stability studies justifying the requested retest period and in accordance with the note for guidance shall be supplied. In accordance with this note for guidance results from accelerated stability studies should be supplied when a retest period is to be mentioned on the certificate. In addition to the retest period, the commercial packaging material and where necessary storage conditions, will also be stated on the certificate. If no request to mention a retest period on the certificate is made stability data may still be submitted in particular to support the discussion on impurities and which should be summarised.

Post-approval Stability Protocol and Stability Commitment (3.2.S.7.2);

A re-test period may be attributed based on extrapolation proposed by the applicant under the conditions described in the NfGs *Stability testing of existing active substances and related finished products* (CPMP/QWP122/02 revision 1) and *Evaluation of Stability Data* (CPMP/ICH/420/02). In this case, and also when the retest period has been based on data obtained on pilot batches, the manufacturer will be asked to supply the complementary and/or additional stability data when available.