<Co>Rapporteur day 80 critical assessment report (Article 10.1 or 10.3)

Quality – generic/hybrid medicinal products

<(Invented) Name>

<(Active Substance)>

EMEA/H/C/xxx

Applicant:

| CHMP Rapporteur:  |  |
| --- | --- |
| <CHMP Rapporteur:> |  |
| EMA PL: |  |
| Start of the procedure: |  |
| Date of this report: |  |
| Deadline for comments: |  |

Note to the (Co)[Rapporteurs](https://www.ema.europa.eu/en/glossary/rapporteur%22%20%5Co%20%22One%20of%20the%20two%20members%20of%20a%20committee%20or%20working%20party%20who%20leads%20the%20evaluation%20of%20an%20application.%22%20%5Ct%20%22_blank): Assessment reports and comments should be circulated VIA **EUDRALINK**. Product Shared Mailbox: product.name-xxxx@ema.europa.eu and product initial MAA dedicated mailbox: MAAxxxx@ema.europa.eu (xxxx refers to the product number EMA/H/C/xxxx) should always be copied.

**Guidance text** is in green italics. You may print a copy of this template with the drafting note, then delete them all in one go:

Click on Ctrl-Alt-Shift-S to view the “styles” window. Select “Drafting notes (Agency)” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

Do not change or delete the titles and the numbering style. (Add “Not applicable” if necessary)

Suggested font: Verdana 9.

Paragraph tab: alignment: left, outline level: body text, indentation: 0, spacing before: 0pt and after: 7pt; line spacing: at least, at: 14pt.

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Administrative information

|  |  |
| --- | --- |
| **Invented name of the generic/hybrid medicinal product:** |  |
| **INN (or common name) of the active substance(s):** |  |
| **Active substance(s):** |  |
| **Applicant:** |  |
| **Applied Indication(s):** |  |
| **Pharmaco-therapeutic group** **(ATC Code):** |  |
| **Pharmaceutical form(s) and strength(s):** |  |
| **Rapporteur contact person:****<Co-rapporteur contact person:>****EMA Product Lead:** | **Name:**Tel: Email:**Name:**Tel: Email:**Name:**Tel: Email: |
| **Names of the Rapporteur assessors** **(internal and external):** | **Quality:****Name(s)**Tel: Email:**Non-clinical:****Name(s)**Tel: Email:**Clinical :****Name(s)**Tel: Email: |
| **<Names of the Co-Rapporteur assessors** **(internal and external):>** | **Quality:**Name(s)Tel: Email:**Non-clinical:**Name(s)Tel: Email:**Clinical:**Name(s)Tel: Email: |

Declarations

This application includes an Active Substance Master File (ASMF):

[ ]  Yes

[ ]  No

[ ]  The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (eg. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received\*.

*\*If the entity from which non-public information originates has consented to its further disclosure, the box should be ticked and there* would *be no need to add details below.*

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

List of abbreviations

GENERAL GUIDANCE

In general the following aspects should be considered:

The report should be sufficiently detailed to allow for secondary assessment by other CHMP experts.

The report should describe salient findings and those deficiencies that justify the questions intended for the applicant. These questions will be listed in the “overview module” of the assessment.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

The report should also emphasise those findings that need to be reflected in the SPC.

The use of tables is encouraged; examples are given in the template and are to be used as appropriate. Tables taken from the dossier may also be appended to the assessment. Don’t forget footnotes!

A separate page has been added in the template for the inclusion of a list of abbreviations, to be completed when necessary.

It is recommended that the font used in the main text be Verdana, size 9.

Link to specific CHMP or CHMP/ICH Notes for guidance as a general framework for guidance: [(http://www.emea.eu.int/index/indexh1.htm)](http://www.emea.eu.int/index/indexh1.htm%29)

Quality critical assessment

The following structure for the quality assessment report of a generic/hybrid product keeps basically to the CTD structure of the dossier, apart from some preliminary sections, e.g. an Introduction section to put the product in context.

Certain Modules in a generic/hybrid dossier may be abridged (e.g. Modules 4 & 5) but this option does not apply to the Quality Module 3 which must be complete. The norm is that a generic/hybrid product should be assessed primarily on its own merits, i.e. as a stand-alone dossier.

The legislation does not require the generic product to be identical to the reference product. While the active substances must be the same with regard to qualitative and quantitative aspects, certain differences may exist particularly with regard to composition of the product (excipients), impurity profiles, etc. It is useful to record such observed differences for information. However, some assessors reserve the right to obtain additional relevant quality information from the dossier of the authorised reference product where necessary, in order to satisfy themselves on matters of concern.

Please also refer to the CTD guidance text for the applicant – it is not considered necessary to repeat this here, but rather to highlight some additional aspects not specifically detailed in the CTD, for the benefit of assessors. Note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the ‘main’ headings. Assessors may add more, or less, depending upon the complexity of the product. In addition, note also that the CTD terms ‘Drug Substance’ and ‘Drug Product’ are synonymous with the EU legislative terms ‘Active Substance’ and ‘Finished Product’ respectively.

Reference to information, which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product) should be clearly marked as “Confidential” and highlighted using a yellow background. These sections will be removed before the assessment is sent to the applicant.

Like the Rapporteurs’ report for an NCE product, this quality assessment report for a generic should be ‘self-standing’. This may be achieved in two ways:

1) Presenting or copying data which are taken from the applicant’s dossier, followed by the assessor’s own critical assessment of these data, particularly with respect to safety/efficacy consequences and highlighting adherence to specific guidance documents. The heading ‘Assessor’s Comments’ should be introduced as a separator in this case, to avoid confusion

2) Alternatively, this report may consist largely\* of the assessor’s own views with references to the applicant’s own data and/or Quality Overall Summary (QOS). In this case, the assessor’s views are intended to be read in conjunction with the QOS which must be attached. The additional headings for assessor’s comments would not be needed. See specific CHMP or CHMP/ICH Notes for guidance as a general framework for quality assessment, e.g.: The Rules Governing Medicinal Products in the EU, volume 3A [http://www.emea.eu.int/index/indexh1.htm:](http://www.emea.eu.int/index/indexh1.htm) The Notice to Applicants revision incorporating the CTD.

In addition, other multidisciplinary guidelines not indexed under ’quality’ may also be relevant, and certain ‘technical’ legislation may also be relevant, e.g. Directive 89/343/EEC relating to radiopharmaceuticals. In general, assessors should try to relate quality matters to efficacy and safety consequences as much as possible. Matters arising from the scientific evaluation below, which have a bearing on the product information, should also be mentioned (comments on the SPC, Labels & Package Leaflet.).

For Post Approval Change Management Protocols Annex 3 should be used to summarise what has been agreed upon. These protocols may be found under Regional Information, e.g. under “Comparability Protocols”.

Assessors are encouraged to complete the proforma for sampling and testing attached to the end of this template (Annex 2) to assist in the post-authorisation sampling and testing scheme for Centrally-authorised products coordinated by the EMEA Inspections function.

\* a limited amount of the applicant’s data such as flow diagrams, specifications etc. may be copied in, to facilitate the reading of the report.

1. Requests for inspection action prior to authorisation:

GMP inspections

Pre-approval inspection for human medicinal products are requested in accordance with Article 8(2) of Regulation (EC) No 726/2004 and Article 111(1) of Directive 2001/83/EC.

Inspections may be carried out to verify compliance with European Union Good Manufacturing Practice principles and guidelines and/or to cover product or process related issues arising from the assessment of the application. Inspections may cover the following activities:

**Manufacture of active substance**

Directive 2001/83/EC as amended requires that pharmaceutical manufacturers use only active substances which have been manufactured in accordance with GMP. The GMP Basic Requirements for Active Substances used as Starting Materials have been introduced as a Part II to the EU GMP guide (EudraLex Vol. 4). It is now the responsibility of the pharmaceutical manufacturers to ensure that the active substances which they use as starting material have been manufactured in compliance with the EU GMP rules (see also Application Form Annex 5.22 in Module 1 which has to contain a relevant statement from the Qualified Person).

An inspection of an active substance manufacturer can be triggered by product or process related issues arising from the evaluation of the dossier. It can also be requested in cases described in the Compilation of European Union Procedures on Inspections and Exchange of Information - Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials.

http://www.ema.europa.eu/docs/en\_GB/document\_library/Regulatory\_and\_procedural\_guideline/2009/10/WC500004706.pdf

For sterile active substances and in most cases based on risk for biological active substances please refer to the requirements outlined for finished product manufacturing sites (below).

**Manufacture of finished product**

**Sites located in the EEA:**

Where a manufacturing site is located in the EEA it is normally not necessary to request an inspection to confirm its GMP status as it is required to be regularly inspected by the relevant authorities by virtue of holding a manufacturing authorisation.

A valid MIA covering the proposed activities is sufficient proof of GMP compliance for sites located in the EEA. GMP certificates older than 3 years are considered valid in connection with a valid MIA.

**Sites located outside the EEA:**

An inspection will normally be requested to confirm the GMP compliance status of manufacturing sites in third countries unless satisfactory information is available from an inspection of the same or similar category of product carried out during the last 2-3 years by an EEA competent authority or by the competent authority of a country where a MRA is in operation, when applicable.

**In all cases** (for sites in the EEA and third countries), an inspection may be requested to cover product or process related issues arising from the assessment of the application. In this case please provide the inspection team with a list of questions/issues, which should be addressed during the inspection.

**Importers and manufacturers responsible for batch release – Site located in the EEA:**

Importing sites in the EEA are required by the provisions of title IV of Directive 2001/83/EC as amended, to hold a manufacturing authorisation. Inspections of importing sites to confirm their GMP compliance status are not normally requested in connection with applications for marketing authorisations. Inspections may however be requested to cover product or process related issues arising from the assessment of the application. In this case please provide the Inspection Team with a list of questions/issues, which should be addressed during the inspection.

If you are recommending an inspection, please consider also your proposal for the inspection team. The inspection team will be drawn from the inspection services of the Supervisory and/or other competent authorities of the EEA. On the advice of the Rapporteur and/or Co-Rapporteur the Inspection Team may include scientific experts and/or a Rapporteur for the Inspection as referred to in the provisions of Article 8 of Regulation (EC) No 726/2004.

As inspections take time to organize, if you are recommending an inspection, please inform the GMP PTM via email by D80 at the latest.

If a pre-approval inspection is requested please refer to the pre-approval inspection in this section of the D80 assessment report. If the inspection was requested to cover product- ore process related issues, please outline briefly in this section the reasons for the request. In addition, we advise that at D120 a major objection should be raised in relation to the pre-approval GMP inspection and the applicant should be asked to provide confirmation of GMP compliance for the site.

**Pre-authorisation sampling and testing**

In accordance with Council Regulation (EEC) No. 726/2004 Article 7(b).

If the evaluation of the dossier gives reason for requesting pre-authorisation sampling and testing, please define the testing scope taking into consideration at least the following items:

- type of samples (e.g. API, finished product)
- number of samples to be analysed
- number of batches to be analysed
- tests to be carried out
- which testing laboratory should be assigned
- deadline for reporting of the results
- contact person at the testing laboratory

If assistance is needed to identify a laboratory, please contact the GMP PTM at EMA (Manufacturing and Quality Compliance Service) who can provide assistance within the framework of the EMA sampling and testing programme.

1. Introduction

General background of the product.

* Brief description of the product type (active substance, pharmaceutical form, container, radiopharmaceutical, herbal, etc.)
* Indications, target population, posology (with regard to the ability of the product to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device).
* Mention any potential structural similarity conflicts with pan-EU authorised OMPs, if detected.( Note that a detailed report on structural similarity conflicts will be prepared separately, as part of the general report of similarity, at day 90 according to the current procedural guidance).
* Preparation/reconstitution of product (e.g. radiopharmaceuticals, lyophilisate).
* Other special features of the product such as delivery or administration systems, medical devices etc.
* Linked or related applications (e.g. drug of a pro-drug, line- extension, simultaneous or ‘double’ applications).

The information provided here is intended to provide a brief description of the main features of the product. The amount of information provided will depend on the nature of the particular product. The clinical context of use should also be briefly mentioned.

|  |  |
| --- | --- |
| Name: |  |
| Dosage form and strength: |  |
| Procedure: |  |
| Therapeutic class or indication: |  |
| Proposed dosage range: |  |

1. Drug substance

- It should be mentioned whether a CEP or ASMF procedure or full information in the dossier of the AS in the dossier is used. The assessment of this closed or restricted part dealing with information which is protected by intellectual property rights or which is otherwise sensitive should be done in a separate report, together with a separate list of questions arising from this report, attached as an Annex.

In case the ASMF procedure is used it should be mentioned that the assessment of the Active Substance Master File (ASMF) is provided in a separate ASMF Assessment Report with a confidential annex on the Restricted Part.

- Mention the EU ASMF reference number in this report.

- Where there is more than one ASMF cited in the dossier, a separate report is provided for each ASMF

- Letters of Access in relation to specific drug products should be described for the product in question.

- When a CEP or ASMF is used, only section III.4 Control of Drug Substance and III.5 Reference Standards or Materials relating to the product manufacturer need completing, unless the applicant has provided additional data e.g. 3.2.S.7 stability data to support a longer re-test period.

- The questions to the restricted part of the ASMF reports will not be sent to the MAH but only to the relevant ASM/holder of the ASMF.

- Where ASMF or CEP is applicable, clarify the source (applicant or ASMF holder or CEP holder) and level of details to be drafted in the assessment report.

- The assessment of the drug substance in this AR should only address additional information provided by the applicant, which is not included in the open part as provided by the ASMF holder. In case a full dossier for the Active Substance is provided by the applicant the full assessment of the active substance should be included in the day 80 AR.

* 1. General information (CTD module 3.2.S.1)

Nomenclature (CTD section: S.1.1)

At least one sentence to mention the name. Confirm whether the name is rINN, or Common Name, etc. State the IUPAC Chemical name, CAS registry etc.

|  |  |
| --- | --- |
| International non-proprietary name (INN): |  |
| United States Adopted Name (USAN): |  |
| Chemical names: |  |
| Other name: |  |
| CAS registry number: |  |
| Laboratory code: |  |
| Molecular formula: |  |
| Relative molecular mass: |  |

Structural formula (CTD section: S.1.2)

Include this and link to similar compounds, by description or by structure.

General properties (CTD section: S.1.3)

|  |  |
| --- | --- |
| Physical characteristics: |  |
| Solubility: |  |
| pKa-value: |  |
| Partition coefficient: |  |
| Hygroscopicity: |  |
| Stereochemistry: |  |
| Polymorphism |  |

Indicate crucial properties relevant to the performance of the product in the clinic and give values, e.g., pKa, solubility, etc. where relevant.

• State if there is a PhEur monograph for the active substance(s)

• State the source of the information on the active substance, e.g. CEP or AS Master File• Mention if the active substance is present as a different salt, ester, complex, etc. than the active substance in the reference product.

Assessor’s comments on S.1 General Information

* 1. Manufacture (CTD module 3.2.S.2)

Manufacturer(s) (CTD section: S.2.1)

The name, address and responsibility of each manufacturer, including contractors, involved in the manufacturing and testing should be provided.

A QP declaration for EU GMP compliance should always be provided, and include all relevant sites. Normally, the use of the template EMA/334808/2014 is expected. Any deviations from the requirements on QP declarations should be commented on.

GMP

Description of manufacturing process and process controls (CTD section:S.2.2)

* Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.
* Relevant process parameters and amounts of materials, reagents and solvents should be laid down in the process description with set points or ranges. The set points and ranges should be justified by process development. Alternatively, the set points used during process validation could be accepted without further justification. Are significant process parameters missing from the description? Has the applicant justified the proposed ranges? “Ranges” only defined by an upper or a lower limit should also be considered. Comment on any other elements of the control strategy, i.e. in-process controls that supplement the process description to assure active substance quality.
* Mention if the proposed starting material(s) is acceptable or not including the scientific reasoning for this. Comment on any experiments performed in order to gain additional process knowledge and understanding, e.g. purge studies.
* Indicate proposed commercial batch size and discuss batch size from batches provided, if necessary.
* Alternate processes – if mentioned, include comment.
* Reprocessing – if mentioned, include comment (e.g., when could this occur). Comment on any reasoning why reprocessing should be described in the dossier instead of handled under GMP.
* Catalysts and solvents - include comment if not in the main application (but in ASM Restricted part of an ASMF).

Control of materials (CTD section: S.2.3)

State adequacy/extent of proposed specifications with particular mention of control of all impurities (including solvents), which might influence the quality of the active substance, especially if the impurities are not controlled in the ASS. Comment if of biological origin.

Control of critical steps and intermediates (CTD section: S.2.4)

Discuss the adequacy of the proposed process control.

Process validation and/or evaluation (CTD section: S.2.5)

Brief summary of the extent of data and results, where relevant. Process validation data and/or evaluation studies for aseptic processing and sterilisation should be provided.

Manufacturing process development (CTD section: S.2.6)

Brief summary of the extent of data and results with reference to substance used preclinical/clinical studies if applicable.

Is a Design Space being proposed? Has the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes of the active substance been established in a multivariate manner? If a Design Space is proposed please consult Annex III.

In general, critical statements are needed on the adequacy of the description of the synthesis, of the control of the materials and intermediates, reproducibility of the manufacturing process identifying those issues not adequately covered and which need to be addressed in the LoQ (with reference to number if wanted). Identify ‘Major’ issues Manufacturer(s) (CTD section: S.2.1)

Assessor’s comments on S.2 Manufacture:

* 1. Characterisation (CTD module 3.2.S.3)

The generic dossier should be regarded as a ‘stand-alone’ dossier, and is assessed on its own merits like any other dossier:

- Application of ICH / PhEur principles

- Below threshold – OK, no problem

- Above thresholds – Identification. Qualification, either by tox. studies or by other means in the current ICH guideline

- Concerning qualification, the generic applicant must provide this justification in their dossier and this should be summarised in the report

- comparative data between generic and reference products for impurities above the qualification threshold may be available in some cases, and are of course useful in the context of “qualification by use”, but these comparative data should be provided by the generic applicant in their dossier. The assessor does not normally look into the dossier of the reference product in order to look for supplementary information which is not present in the generic dossier. In this regard, the generic applicant has to submit a comprehensive dossier demonstrating the suitability of the product for its intended purpose. It is not the assessor’s responsibility to justify the suitability of the product, but to assess if the information provided by the applicant is adequate.

• For radiopharmaceuticals, mention also radiochemical purity and radionuclidic purity.

Elucidation of structure and other characteristics (CTD section: S.3.1)

• Elucidation of structure and other characteristics: Summary of methods used to elucidate the structure and characterise properties of the active substance, e.g., chirality, polymorphism, etc.

• In the case of radiopharmaceuticals, it should be made clear what the active substance is considered to be, i.e. unlabelled ligand, radiolabelled substance, or radiolabel for labelling of another ‘carrier’ molecule. (In this latter case information is normally included in the ‘carrier’ dossier).

• In general, critical statements are especially needed on the issue of whether or not methods used for elucidation of structure are adequate.

Impurities (CTD section: S.3.2)

• Impurities: emphasise process-related impurities & degradation products, solvents, reagents, etc. here. Maybe use text in QOS for summary tables of these data (degradation products may be discussed under stability data S.4.).

• Differentiate, when possible, between process related impurities and impurities resulting from the degradation of the API.

• Qualification of generic impurities: normally, the existence of a CEP or compliance with a PhEur monograph would generally be taken as indicating the satisfactory quality of the active substance. In the absence of a PhEur monograph, ICH principles should be applied.

• Conclusion on the adequacy of the company’s approach to the control and qualification of impurities, with particular reference to non- clinical (toxicology) studies (and clinical studies where relevant).

Assessor’s comments on S.3 Characterisation:

* 1. Control of drug substance (CTD module 3.2.S.4)

Specification (CTD section: S.4.1)

Table of specification to be inserted. Provide a compiled specification when there are more than one sources of the active substance having different specifications. Concerning impurity levels in the specification see also the notes under III.3 (Impurities S.3.2)

Table S. 4-1. Specifications

| Specification parameter | Test method | Test limits |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

Analytical procedure (CTD section: S.4.2)

Combine in above table – just refer to method. If relevant for the context the principle may be described in more detail. Is any analytical method flexibility described?

Validation of analytical procedure (CTD section: S.4.3)

State if in accordance with ICH or not, and mention any deviation. If necessary, e.g. in order to highlight significant deviations or to highlight validation results, a table may be used (see D80 AR template).

• Are the methods adequate to control the substance on a routine basis?

Batch analyses (CTD section: S.4.4)

• Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?

Justification of specification (CTD section: S .4.5)

• Is the applicant’s proposed justification of the specification adequate or not, bearing in mind the intended use of the drug substance in the product.

• If real time release testing is proposed, has the applicant demonstrated enhanced product and process understanding? Has the applicant introduced appropriate controls of the critical process parameters and critical materials attributes that would justify real time release testing? When comparing batch results from end product testing and real time testing has the effect of environmental factors been considered? Is a scheme that foresees comparison of end product and real time release testing for a sufficient number of batches per year included? If multivariate models are used to predict the active substance quality attributes or for online process monitoring see Annex III.

Assessor’s comments on S.4 Control of Drug Substance:

* 1. Reference standards of materials (CTD module 3.2.S.5)

• Are reference standard(s) available from EDQM? If not, are in-house reference standard(s) adequately described? (Refer to EP 5.12 Reference standards).

• Make a list of all reference standards required by the analytical procedures and state the type of test the standard is used for (e.g. identification, assay or related substances test). Is the quality of the reference standard acceptable for its use?

Assessor’s comments on S.5 Reference Standards or Materials:

* 1. Container closure system (CTD module 3.2.S.6)

• Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the drug substance?

• Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

• Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the re-test period (ref. S.7).

Assessor’s comments on S.6 Container Closure System:

* 1. Stability (CTD module 3.2.S.7)

Stability summary and conclusion (CTD section: S.7.1)

• State if the studies are carried out in accordance with current ICH/CHMP guidelines. Are there deviations? Are the deviations justified in this case?

• Stability summary and conclusions: Reference to any differences in manufacturing. Processes used, with comments on whether or not this has a significant effect on the stability profile.

• Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.

• Confirm that the analytical methods are stability-indicating (ref. S.4). Stability indicating tests should be chosen, which are able to detect significant changes in the quality of the product.

• Confirm that the containers used in the stability studies are the same as those proposed for routine storage (ref. S.6).

• Are there any trends? A brief summary should be given for the stability data.

• Final conclusion on whether or not the proposed re-test period is justified.

Table S. 7-1. Stability studies

| Temp °C, RH % | n batches x months | Batch size | Package |
| --- | --- | --- | --- |
| 25 °C / 60% RH |  | Production scale / Pilot scale | Intended for marketing |
| 40 °C / 75% RH |  |  |  |
|  |  |  |  |

Post-approval stability protocol and stability commitments (CTD section: S.7.2)

Stability data (CTD section: S.7.3)

The stability data on which the summary and conclusion in S.7.1 is based, is included in the dossier.

Assessor’s comments on S.7 Stability:

1. Drug product (CTD module 3.2.P)
	1. Description and composition of the drug product (CTD module 3.2.P.1)

All components of the presentation as intended for marketing, including reconstitution diluents, medical devices, etc. should be clearly stated.

• The qualitative composition of a generic may be different to the reference product, and the assessor should mention the observed differences for information, assuming they are justified in the generic dossier in the normal way, i.e. with reference to bioequivalence, stability etc.

• In particular where the product presentation includes a medical device, it is important to cross-refer to the details of the device in 3.2.R, Regional Information. Check that any medical devices are CE- marked prior to submission of the dossier for the medicinal product. Has the CE mark been attributed for the intended use?

• Whilst the composition may be obvious, it may be necessary to pay particular attention to the details of the container/closure system, especially for labile or sterile products. The composition of {drug product} is presented in Table P.1-1 below.

Table P. 1-1. Complete composition of XXX

| Ingredient | Reference | XXXAmount (XXX) | XXXAmount (XXX) | Function |
| --- | --- | --- | --- | --- |
|  |  |  |  | Active |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

Assessor’s comments on P.1 Description and Composition of the Drug Product:

* 1. Pharmaceutical development (CTD module 3.2.P.2)

The pharmaceutical development of a generic product should be described and justified according to current EU guidelines.

Components of the drug product (CTD section:P.2.1)

Drug substance (CTD section: P.2.1.1)

• Has the company identified those physico-chemical properties of the drug substance that are clinically relevant for the patient?

• Have these properties been adequately specified and are they adequately controlled?

• On what basis have the limits been justified?

• Where potentially key parameters are not controlled, is the justification for their omission acceptable?

• Use of materials of animal or human origin – have these been justified?

Excipients (CTD section: P.2.1.2)

• Have important, novel or unusual excipients been identified regarding their impact on product performance?

• The applicant’s choice and function of key excipients should be mentioned, e.g. those modifying release or disposition of the drug substance. In some cases (e.g. gas dispersions for diagnostic ultrasound investigations) the total formulation or system is responsible for the clinical efficacy of the product and these cases should be discussed in detail. Is the quantity of the excipients used justified? (preservatives, buffers, etc).

• Assessors should also refer to section V of this report (CTD Appendix 3.2.A.3, Novel Excipients), where a more detailed evaluation of the excipient per se may be given. Note that ‘new’ excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are ‘full’, i.e. manufacture and control, reference to toxicology studies, etc.

Drug product (CTD section: P.2.2)

Formulation Development: is the formulation development based on sound scientific principles?

Formulation development (CTD section: P.2.2.1)

* Has the applicant presented the Target Product Profile of the product, i.e. the quality characteristics that the product should have to ensure the desired quality taking into account safety and efficacy? Is the formulation development supported by clinical development? Discussion of bioequivalence between commercial formulation and clinical trial formulations, if different. Discuss if possible differences in finished product quality attributes (e.g. impurity and dissolution profile).
* Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties. Results of studies to establish IVIVC, if relevant.
* Early development formulations for pre-clinical and clinical studies should be highlighted where relevant, and comments made relating to the findings of these studies. Additional details should be given if the development encompasses a paediatric formulation including information for which age group this is intended, if appropriate.
* In case of scored tablets, has relevant testing of the efficacy of the break-mark(s) according to Ph. Eur. Tablets; Subdivision of tablets been performed?

Bioequivalence study and reference product / Clinical formulation

Overages (CTD section: P.2.2.2)

On which basis are overages justified?

Physicochemical and biological properties (CTD section: P.2.2.3)

• Are key parameters identified and adequately controlled?

The CTD-Q gives an adequate list of parameters that need to be discussed with regard to their impact on the performance of the product, where relevant. e.g. for tablets – the particle size and polymorphism of an active substance with low aqueous solubility may need to be discussed with reference to their effects on dissolution and bioavailability. In this example the pH-solubility profile would also be relevant basic information having an impact on the choice of dissolution test methodology.

Manufacturing process development (CTD section: P.2.3)

• If the manufacturing process of the product influences the physicochemical properties of the drug substance (e.g. polymorphic form), check that the studies carried out on the drug substance remain valid.

• Has the choice of process been justified, where necessary? Are critical process parameters, relevant for subsequent process validation, identified? Are process parameter ranges satisfactorily investigated/supported by pharmaceutical development? Are differences in the manufacturing processes of the commercial product and clinical trial material adequately explained and discussed? Does the process compensate for the variability in the material attributes? The identification of the critical process parameters may be performed on an empirical basis or through systematic evaluation using risk assessment methodologies and statistically designed experimentation. In the later case please consult Annex III.

Container closure system (CTD section: P.2.4)

• Is the choice of materials for the container and closure adequate to support the stability and use of the product with its targeted patient group (e.g. elderly, child resistant)?

• Technical properties of the container closure system with respect to patient use should be considered, e.g. nasal sprays, inhalers, prefilled syringes.

Microbiological attributes (CTD section: P.2.5)

• Is the use of additives, e.g. preservatives and antioxidants justified regarding their concentration and nature?

Compatibility (CTD section: P.2.6)

• Do the compatibility studies support the instructions for use and handling in the SPC?

Assessor’s comments on P.2 Pharmaceutical Development:

* 1. Manufacture (CTD module 3.2.P.3)

Manufacturer(s) (CTD section: P.3.1)

• The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing and testing should be provided.

• Where the product consists of the active substance without excipients details of the manufacturers should also be referred to here and should be accordingly licensed.

Batch formula (CTD section: P.3.2)

• Where ranges of batch size are proposed for production, blending of batches or the use of sub batches, the acceptability should be addressed. Discuss the bath size(s) of the data provided.

Description of manufacturing process and process controls (CTD section: P.3.3)

• Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.

• Relevant process parameters should be laid down in the process description with set points or ranges. The set points and ranges should be justified by pharmaceutical development. Alternatively, the settings used during process validation could be accepted without further justification. Are significant process parameters missing from the description? Has the applicant justified the proposed ranges? “Ranges” only defined by an upper or a lower limit should also be considered. Comment on any other elements of the control strategy, i.e. in-process controls, that supplement the process description to assure product quality.

• Has the applicant introduced controls to monitor real time the critical material attributes and critical process parameters? Do the controls reduce the risks identified during formulation and process development? Are there feedback loops in place that allow adjustment of the process to compensate for the variability observed?

• Is a Design Space being proposed? Has the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes been established in a multivariate manner? If a Design Space is proposed please consult Annex III.

• The assessor should discuss any specialised processes that may need to be inspected (see preamble to this report).

• Confirm that process holding times and transport arrangements are relevant and have been justified / validated.

Controls of critical steps and intermediates (CTD section: P.3.4)

• Has the applicant introduced controls to monitor real time the critical material attributes and critical process parameters? Do the controls reduce the risks identified during formulation and process development? Are there feedback loops in place that allow adjustment of the process to compensate for the variability observed?

Process validation and/or evaluation (CTD section: P.3.5)

• The assessor should comment here on whether process validation data are needed in the dossier (i.e. whether it is needed prior to authorisation). Where non-standard methods are used these validation data would normally be expected. For standard processes the process validation scheme referred to in 3.2.R Regional Information should be evaluated.

• Any proposals for continuous process verification should be supported by adequate development data and an appropriate control strategy that allows real time monitoring of the critical process parameters and material critical quality attributes.

• Any requests for ‘real time release testing’ need to be fully evaluated and commented on here, with a comment from the GMP Inspectors, where necessary, in accordance with the CHMP NfG.

Assessor’s comments on P.3 Manufacture:

* 1. Control of excipients (CTD module 3.2.P.4)

• If PhEur monograph exists, mention may be brief and should be enough in most cases.

• If non-PhEur, is the specification adequate?

• Do the specifications and tests reflect the functionality in a relevant way? Especially in novel delivery systems, some ingredients may have a special function, and should be described and controlled in more detail, especially with regard to functionality testing.

• Note that ‘new’ excipients not present in products authorised in the EU may be treated as new active substances and data requirements are ‘full’, i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed under section V of this report, CTD-Q Appendix A3 below)

Specifications (CTD section: P.4.1)

Analytical procedures (CTD section: P.4.2)

Validation of analytical procedures (CTD section: P.4.3)

Justifications of specifications (CTD section: P.4.4)

Excipients of human and animal origin (CTD section: P.4.5)

Novel excipients (CTD section: P.4.6)

Assessor’s comments on P.4 Control of Excipients:

* 1. Control of drug product (CTD module 3.2.P.5)

Specification(s) (CTD section: P.5.1)

• Release and shelf life specifications should be presented side by side in tabular form, with brief reference to the method used.

• If relevant for the context the principle may be described in more detail. Is any analytical method flexibility described?

• If real time release testing is proposed, has the applicant demonstrated enhanced product and process understanding? Has the applicant introduced appropriate controls of the critical process parameters and critical materials attributes that would justify real time release testing? When comparing batch results from end product testing and real time testing has the effect of environmental factors been considered? Is a scheme that foresees comparison of end product and real time release testing for a sufficient number of batches per year included? If multivariate models are used to predict finished product quality attributes or for online process monitoring see Annex III.

• Specification summary, important tests, particularly relating to bioavailability/efficacy (e.g. dissolution, particle size, polymorphism if relevant.) and safety (impurities or sterility, pyrogens etc. for sterile products). The general relevance of the release specification should be discussed considering the method of manufacture and clinical use, route of administration etc.

• For radiopharmaceuticals, a discussion of radiochemical purity of reconstituted ‘cold’ kits should be discussed, where relevant.

Table P. 5-1. Release and shelf-life specifications

| Specification parameter | Test method | Test limits |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

Analytical procedures (CTD section: P.5.2)

Validation of analytical procedures (CTD section: P.5.3)

• Validation of analytical procedures: State if in accordance with ICH or not, and mention any deviations. (All control methods, regardless of whether they are applicable to control at release or to the shelf life should be discussed here, under P.5). If necessary, e.g. in order to highlight significant deviations, a table may be used.

Batch analyses (CTD section: P.5.4)

• Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?

Characterisation of impurities (CTD section: P.5.5)

• Note that the tests for impurities in the product specification should focus on degradation products arising from the manufacturing process and those expected during storage, rather than manufacturing process-related impurities carried over in the drug substance if these are controlled in the drug substance and do not change in the product during storage.

• impurities/degradants in generic products:

See the comments under III.3 of this report (CTD S.3.2 impurities in the active substance).

The same principles apply here in relation to impurities/degradants in the product.

Justification of specification(s) (CTD section: P.5.6)

Assessor’s comments on P.5 Control of Drug Product:

* 1. Reference standards or materials (CTD module 3.2.P.6)

• Are reference standard(s) available from EDQM? If not, are in-house reference standard(s) adequately described? (Refer to EP 5.12 Reference standards).

• Make a list of all reference standards required by the analytical procedures and state the type of test the standard is used for (e.g. identification, assay or related substances test). Is the quality of the reference standard acceptable for its use?

Assessor’s comments on P.6 Reference Standards or Materials:

* 1. Container closure system (CTD module 3.2.P.7)

• Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the product?

• Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

• Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life. (ref. CTD.3.2.P.8).

Assessor’s comments on P.7 Container Closure System:

* 1. Stability (CTD module 3.2.P.8)

Stability summary and conclusion (CTD section: P.8.1)

• State if the studies are carried out in accordance with current ICH/CHMP guidelines. Are there deviations? Are the deviations justified in this case?

• Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.

• Bracketing & Matrixing designs – acceptable?

• Are the methods used the same as or different to those described in

P.5? Are they well validated and shown to be stability indicating?

• Confirm that the containers used in the stability studies are the same as those proposed for routine storage.

• Note that the qualification of impurities carried out on the active substance may not necessarily address degradants induced by the product matrix or product manufacturing process, and this may need to be addressed with reference to other nonclinical studies if necessary. In addition, apart from degradation products, other product characteristics may change on storage and these need to be justified with reference to the preclinical and clinical results.

• Are there any trends? A brief summary should be given for the stability data including findings that could be useful as a basis for the EPAR. Since limited information is included in the SPC, other relevant stability information should be included in the EPAR (including any in-use stability studies).

• Confirm if the proposed shelf life and storage conditions are adequate.

In–Use stability:

• Comment also on stability after opening and during use, e.g. for infusions to be diluted, stability after dilution and during administration, compatibility with commercially available administration equipment, etc. Are an in-use shelf life and storage conditions necessary? Are the applicant’s proposals in line with the current guidelines? If not, are they still justified?

• For radiopharmaceuticals, a discussion of user-reconstitution methods for ‘cold’ kits may be discussed here, together with a discussion of post-reconstitution stability.

General:

• Are all of the above considerations correctly reflected in the SPC/package leaflet? Assessor should make a conclusion on whether or not all shelf lives and storage conditions defined inthe SPC are justified.

| Temp °C, RH % | n batches x months | Batch size | Package |
| --- | --- | --- | --- |
| 25 °C / 60% RH |  | Production scale / Pilot scale | Intended for marketing |
| 40 °C / 75% RH |  |  |  |
|  |  |  |  |

Post-approval stability protocol and stability commitment (CTD section: P.8.2)

Stability data (CTD section: P.8.3)

The stability data on which the summary and conclusion in P.8.1 is based, is included in the dossier.

Assessor’s comments on P.8 Stability:

1. Appendices (CTD module 3.2.A)

Facilities and equipment

Adventitious agents safety evaluation

(When relevant for chemical generics)

Novel excipients

Note that ‘new’ excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are ‘full’, i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed here)

1. Regional information

Process validation scheme for the drug product

Medical device issues

Where the presentation of the medicinal product includes elements which are classified as medical devices (e.g. needles, catheters, etc.), these must be CE-marked prior to submission of the dossier and a statement on compliance with the relevant medical devices legislation is required. Otherwise, to complete the evaluation of the product as a whole, the medicines competent authority has to consult with a medical devices competent authority in order to verify the acceptability of the device element with regard to EU requirements. In addition, for those cases where the device may not be so simple, but may in fact be a complex delivery system (e.g. transdermal iontophoretic delivery system included in the total presentation) an evaluation report on the device aspects in relation to the clinical performance of the product as a whole would also be necessary.

TSE Issues

1. Assessor’s comments on the SmPC, labels and package leaflet

Please, comment on following sections if appropriate

SmPC

|  |  |
| --- | --- |
| 2. Qualitative and Quantitative Composition |  |
| 3. Pharmaceutical Form |  |
| 4.2 Posology and method of administration(e.g. terminology used for oral liquids) |  |
| 4.4 Special warnings and precautions for use (i.e. warnings necessary for excipients or residues) |  |
| 6.1 List of excipients |  |
| 6.2 Incompatibilities |  |
| 6.3 Shelf life |  |
| 6.4 Special precautions for storage |  |
| 6.5 Nature and contents of the container |  |
| 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product |  |
| 11. Dosimetry (if applicable) |  |
| 12. Instructions for preparation of radiopharmaceuticals (if applicable) |  |

1. Assessor’s overall conclusions on quality

The content of this paragraph could be carried forward to the “Overview module” of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In relation to the Quality aspects impacting the Benefit-Risk balance, indicate if there is any quality aspect either in the active substance or in the finished product which could lead to impact on the Benefit- Risk Balance.

Indicate if a paediatric formulation has been developed or is to be developed. Indicate in which paediatric age groups the formulation would be used.

As an alternative this section could simply state the main conclusions, in which case the text in the “Overview module” has to be elaborated on separately.

1. List of questions as proposed by the rapporteur

Definitions of questions:

“Major objections”, preclude a recommendation for marketing authorisation. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action from the applicant.

“Other concerns”, may affect the proposed conditions for marketing authorisation and product information. Other concerns should be resolved before approval. Failure to resolve other concerns may render the application un-approvable.

In general, subheadings should be used where necessary throughout the list, to collect objections and concerns in relevant groups.

This list should be carried forward to the “overview module”.

Also, state whether or not there is a need for a GMP inspection. Where an inspection has already been requested this should be stated.

Quality aspects

Major objections

Drug substance [related to additional data provided by applicant only]

Drug substance [applicant’s part as provided by ASMF holder]

Note: In case the ASMF procedure is used the following should be stated in case Major Objections are being raised on the restricted part of the ASMF:

“For Major Objections on the restricted part of the ASMF see separate AR on the ASMF”

In addition, it should, as far as possible, be mentioned what these Major Objections concern without revealing any details.

Drug product

Other concerns

Drug substance [related to additional data provided by applicant only]

Note: When applicable: “For Other concerns on the restricted part of the ASMF see separate AR on the ASMF”

Drug product

1. ANNEX 1 (as appropriate)

Active Substance Master File (ASMF) Assessment Report(s) – in separate document(s).

1. ANNEX 2 (For centrally – submitted product)

Proposals for post-authorisation Sampling and Testing

**Selection of parameters for testing during post authorisation surveillance for centrally authorised products**

EMA manages annual sampling and testing programmes for centrally authorised products in accordance with Art. 57r of Regulation (EC) 2004/726 in conjunction with the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Official Medicines Control Laboratories of the EU/EEA Member States.

The rapporteur’s recommendations for the parameters to be tested should be included on the attached form. Recommendations should be focused on the finished product and should be as precise as possible. Whenever several methods are applicable to a parameter, the method(s) used should be clearly specified. Assessors are recommended to discuss the selection of parameters to be tested with colleagues from the OMCL of the rapporteur’s country.

Parameters indicative of the overall quality of the product such as appearance, weight or volume, dissolution, pH, moisture content particle counts, osmolality and disintegration are readily performed by OMCLs.

Usually active-specific assays and impurity tests provide sufficient information on the identity of the active substance and the need for additional specific identity testing should be justified.

When bioassays are requested it should be noted that these are often very challenging for OMCLs to repeat in a proficient manner but should normally be requested when it is the only means to verify the concentration of the active, or where there is other justification.

It should also be noted that occasionally the use of laboratory animals is required.

Owing to the limitations of the test itself and the non-availability of appropriate samples, requests for sterility testing is not recommended as part of routine post-authorisation surveillance.

The form allows you to record also recommendations for the testing of the active substance. However, testing of active substances should only be requested where justified e.g.:

potential safety problems with impurities arising from the process;

stability problems (if this cannot be covered adequately by the testing of the finished medicinal product);

the active ingredient is too diluted in the finished medicinal product so that an important parameter cannot be tested;

matrix problems that prevent testing an important parameter in the finished medicinal product.

The selection of products for inclusion in any annual sampling and testing programme is largely driven through a risk based approach as agreed by CHMP in January 2008 (EMEA/INS/S&T/81176/2007). The second page of the attached form allows the assessor to assign weightings based on his/her detailed assessment of the quality part of the dossier which will then be used by EMA in the risk ranking model used for the selection of products for testing in any one annual programme.

It is understood that if any of these risk factors are deemed to apply that the assessor will nevertheless have satisfied himself, if necessary by seeking further information from the applicant, that the product meets the necessary quality standards for the grant of a marketing authorisation. The intention is simply to give the assessor the opportunity to influence the weighting assigned to the product in the context of the sampling and testing scheme should it be felt appropriate. Each box checked will assign a weighting value. Any number of boxes can be checked as appropriate.Doc. Ref: EMEA/INS/3924/02 Proposals from the Rapporteur / Co-Rapporteur[[1]](#footnote-2) on “Essential Quality Parameters to be tested for the Control of Marketed Centrally Authorised Product”

|  |  |
| --- | --- |
| **NAME OF MEDICINAL PRODUCT** **- - - - - - - - - - - - - - - - - - - - -** | Application number:EMEA/ / / |
| Authorisation number:EU/ /  |
| **Active substance****- - - - - - - - - - - - - - - - - - - - -** | [ ]  NCE[ ] Other |
| **Active substance****(please see guidance given above)**[ ]  No control[ ]  Identity[ ]  Assay / activity[ ]  Purity (Main impurities - Manufacturing)[ ]  Other parameters | Rationale for testing[[2]](#footnote-3)*(specification and test method, when appropriate)*………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………… |
| **Following a critical review the following quality test parameters have been selected for testing by OMCLs during post-authorisation surveillance** |
| Medicinal Product[ ]  No control[ ]  Identity[ ]  Assay / activity[ ]  Purity (main impurities - stability)[ ]  Dissolution[ ]  Uniformity of dosage units[ ]  Moisture Content[ ]  Other parameters | Comments*(specification and test method, if several methods are possible for a parameter please specify which method(s) should be applied)*……………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………………… |
| **Recommendation, when applicable, on pharmaceutical form / strength / presentation to be tested**  |

|  |
| --- |
| **Please record below the name, organisation and telephone number of a contact person**  |
| Name: |  |  |
| Organisation: |  |  |
| Telephone Nr.: |  |  |
|  |  |  |

Assessor-identified weighting factors to be taken into account in the risk-based selection of products for testing

[ ]  An inherent variability in the production process

[ ]  Inherent difficulties foreseen with the testing methodology

[ ]  Novel manufacturing or control technology[[3]](#footnote-4)

[ ]  Potential presence of toxic impurities

[ ]  A particular risk of bioavailability problems

[ ]  A particular risk inherent in the manufacturing or control methodology not covered by any of the above(explanatory comments may be made below).

…………………………………………………………………………………….

…………………………………………………………………………………….

[ ]  None of the above weighting factors apply

1. Annex 3 (Draft)

The purpose of this Annex is to highlight issues that should be reflected in the assessment report concerning the evaluation of risk assessment methodologies and statistical tools that are used in the context of ICH Q8, ICH Q9 and Q11 (draft) Guidelines. Assessors are encouraged to read this annex in conjunction with any related Guidelines.

1. Risk assessment methodologies

Risk assessment tools can be used in many situations. For instance it may be used to rank and select material quality attributes and /or process parameters that should be within appropriate ranges to ensure the desired product quality. Such tools could also be used to select process parameters that may potentially impact product quality based on prior knowledge and experimental data. Issues that need to be taken into account in the evaluation include:

• Has a summary of all material quality attributes and process parameters that based on previous knowledge and/or experimental data may have an impact on product quality been presented?

For FMEA analyses:

• Have all the relevant known risk factors been included? e.g. known risk factors of the finished product (e.g. degradation, solubility etc)

• Has the effect of unit operations and material properties been included?

• Has the applicant explained how the risk ranking and scoring has been performed?

• Has the applicant justified how the threshold has been set in order to select, which parameters will be further studied?

• Do you agree with the proposed risk ranking?

• Is the result of the FMEA in accordance with existing scientific knowledge? If not has it been justified?

• Are the identified risks managed by the Design Space or the proposed control strategy?

2. Design of Experiments

Design of Experiments (DoEs) is a strategy for experimentation, whereby all factors under study are varied at the same time in accordance to rigorously formulated mathematical protocols. The goal is to generate representative and informative experiments that maximise the information provided with the minimum number of experiments. The factors to be studied in a DoE should come out of the risk assessment exercise. A full statistical evaluation of DoEs performed at early development stages (e.g. for screening) is not necessary. A narrative description of the factors and levels studied and the conclusions reached is adequate.

However for DoEs used for the establishment of CQAs, CPPs and / or a

Design Space:

The following data should be considered:

• Type of experimental design used and justification of its appropriateness (e.g. some screening designs are not appropriate since they cannot identify interactions). The power of the design should be stated. (Experimental error compared to the differences in the responses that have to be shown)

• Factors under study and their ranges (in a tabular format if possible)

• The list of design runs clearly stating the batch or study number and the scale of the batch involved in each run. The number of replicated runs should be mentioned.

• Reference to the analytical methods used for the evaluation of the data and demonstration of their suitability for their intended use.

• Statistical results (e.g. Pareto diagrams or a simple list of the sizes of effects and interactions) showing the relative significance of the factors under study as well as of the interactions between them (where applicable) should be provided

• Ensure that the predictions made from a DoE study are appropriate for the ranges studied and scale/equipment differences.

3. Multivariate Data Analysis (MVDA) for Multivariate Statistical Process Control (MSPC)

Multivariate data analysis (MVDA) including Principal Components Analysis (PCA) and Partial Least Squares (PLS) can be used to model pharmaceutical processes. PCA is often used for data overview e.g. for detecting groups and trends among observations, for evaluating relationships between variables and between observations and variables. While PLS is used for linking input and response variables together with the aim of predicting one or more components. Issues that need to be taken into account, when MVDA models are used for MSPC include:

• Are the spectral sample preparation and the reference analytical method used to analyse the sample fit for purpose? For online or in- line control where there is no sampling: what is the repeatability and the reproducibility of the sampling in combination with the analytical method?

• Are the validation (training) and calibration (test) datasets representative of the expected process variability? Has the applicability of the model been demonstrated across all the variation allowed by the Design Space? In the cases that this is difficult to show, the results of the risk assessment could be used. The influence of all important risk factors should be checked and included in the calibration, validation and test set.

• Does the variability of the calibration (test) set adequately represent most of the variability of the validation (training) set?

• Have outliers been identified in the original dataset and if yes, is the justification for (non)- omission of data valid? Please note that if the dataset used to develop the model is generated from a DoE, the omission of data may have a greater impact on the predictive power of the model compared to historical datasets.

• Is the information concerning the pre-treatment of data (if any) adequately described and consistently applied for all datasets used for creation, optimization and validation of the model?

• Are the MVDA modelling techniques adequately described including a brief justification for the selection of the selected algorithm?

• Do you agree with the selection of the variables that have been included in the model? Compare with the results of the risk assessment. Are there any relevant sources of variation not included in the model and if yes, is this justified?

• For PLS models, is the model fit for purpose? Is the complexity of the model optimal? Note: the PLS model complexity usually corresponds to the number of PLS (latent) factors resulting in the lowest RMSECV. The model complexity (number of PLS factors used to build the model) should be presented in a graph showing the regression coefficients for each variable

• Can the weightings (high/ low) of the variables in the model be explained with the existing scientific knowledge or rational concerning that variable and/or manufacturing process?

• Is the MVDA model statistically evaluated for fitting and predictive ability? The standard error for prediction should be discussed against the precision of the reference analytical method precision.

• Has a model verification scheme been proposed for the product lifecycle? Has it been defined which criteria would trigger an update of the model and are they adequate?

4. Design Space (DS)

Aspects that may be considered when a DS has been proposed include:

• Has the applicant provided adequate data to support the DS applied for? (Risk assessment, experimental data, models that have been statistically evaluated and verified at full scale)

• In case that the Design Space has been developed at lab or pilot scale, has the applicant demonstrated its validity at production scale through the use of scaling factors or independent experiments, or otherwise has it been demonstrated that the parameters are scale independent? Scaling factors might be supported by literature or prior knowledge. Has the applicant discussed the potential risks in the scale-up operation and is there an appropriate control strategy in place to manage these risks?

• Has the applicant considered all CQAs, when developing a DS? (See risk assessment and DoE results)

• Does the control strategy support the DS?

• Are all critical parameters identified in the unit operation part of the Design Space? If not, is there an appropriate justification?

Design space and change management protocols (if applicable)

This Annex is an extract of the main body of the AR and its purpose is to summarise all aspects agreed upon in the dossier that result to post approval regulatory flexibility. This annex may be used by Inspectors and could be a basis for the evaluation of post-approval variation applications.

1. Active substance

1.1. Design space for the active substance

Presentation of the Design Space (attributes and their ranges) in a tabular format

1.2. Change management protocols for the active substance

(Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change)

2. Finished product

1.3. Design space for the finished product

Presentation of the Design Space (attributes and their ranges) in a tabular format

1.4. Change management protocols for the finished product

(Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change).

1. Delete as appropriate [↑](#footnote-ref-2)
2. A (short) rationale should be provided for each test selected for the active substance. [↑](#footnote-ref-3)
3. Note: PAT or new ICH approaches to quality are expected to lead to enhanced product and process knowledge and improved quality assurance rather than increased risk but it is accepted that assessors may wish to express caution in some cases until there is greater experience and confidence. [↑](#footnote-ref-4)