Harmonisation of quality dossier following Union Referral – Challenges and points to consider with focus on sterile finished products

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List of Abbreviations

BP	British Pharmacopeia
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Control
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CMS	Concerned Member State
CTD	Common Technical Document
DCP	Decentralised Procedure
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FVAR	Final Variation Assessment Report
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.v.	Intravenous
JP	Japanese Pharmacopoeia
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
NTA	Notice to Applicants
QP	Qualified Person
PDE	Permitted Daily Exposure
PL	Package Leaflet

Ph. Eur.	European Pharmacopoeia
PVAR	Preliminary Variation Assessment Report
RH	Room Humidity
RMS	Reference Member State
RSI	Request for supplementary information
SmPC	Summary of Product Characteristics
USP	United States Pharmacopeia
WHO	World Health Organisation

1 Introduction

In accordance with Directive 2001/83/EC [1] different types of referral may be triggered for medicinal products with the aim to resolve issues in case of safety, efficacy or quality concerns and to harmonise the divergences among the different EU countries:

- Article 29(4): “Mutual Recognition and Decentralised Referral”
- Article 30: “Harmonisation Referral”
- Article 31: “Union Interest Referral”
- Article 107i: “Urgent Union Procedure”

The concerned marketing authorisations will be mainly harmonised with regard to their Summary of Product Characteristics, Package Leaflet and Labelling as well as with regard to the related Module 4 (non-clinical dossier) and Module 5 (clinical dossier). If the quality dossier is not part of the referral procedure it is recommended to the Marketing Authorisation Holder (MAH) or applicant to also harmonise the Module 3 after the end of the referral procedure. This in particular applies to nationally authorised products involved in an Article 30 or 31 referral.

In the framework of the quality dossier harmonisation certain regulatory requirements have to be fulfilled in order to create the same regulatory basis for all concerned national marketing authorisations across the EU. In addition the relevant guidelines have to be adhered when preparing the required documentation and submitting the appropriate variation.

Based on the current regulatory, quality and labelling guidelines the competent national Health Authorities review and assess the documentation provided by the applicant. Due to the information that has to be included in the quality dossier and the pharmaceutical sections of the Product Information texts deficiencies in the drug substance and drug product sections of Module 3 as well as in the Labelling might be identified during the evaluation of the variation application.

This master thesis focuses on the different challenges when harmonising the quality dossier following a Union referral and gives a comprehensive overview on the regulatory requirements and relevant items that have to be taken into consideration by the Marketing Authorisation Holders or applicants in this context. The focus is on liquid sterile finished products which are registered nationally in the EU for several years.

Considering the various regulatory requirements and expectations of the Health Authorities the handling of this harmonisation process in a pharmaceutical company is discussed particularly with regard to the required activities at the different procedural stages and the consequences of one approved harmonised dossier in EU.

2 Union Referral Procedures

Union referral procedures can be initiated according to the following articles of Directive 2001/83/EC [1], as amended:

Article 29(4) (“Mutual Recognition and Decentralised Referral”)

An article 29(4) referral has to be initiated by the Reference Member State (RMS) during a Mutual Recognition (MRP) or Decentralised Procedure (DCP) due to a “Potential Serious Risk to Public Health” when the disagreement between the Member States on the assessment report and Product Information (Summary of Product Characteristics, Package Leaflet and Labelling) proposed by the RMS cannot be resolved within the 60 days coordination group procedure (as laid down in Article 29(1) to (3) of Directive 2001/83/EC). A “Potential Serious Risk to Public Health” is defined in the relevant guideline by the EU Commission [2]. Only the medicinal product assessed in the MRP or DCP is involved in this referral [3].

Article 30 (“Harmonisation Referral”)

An Article 30(1) referral can be triggered by the EU Commission, a Member State, the Marketing Authorisation Holder or the applicant in case of divergent decisions in more than two Member States on the marketing authorisation (e.g. with regard to indications, contraindications, posology or warnings), withdrawal or suspension of a certain medicinal product in order to resolve divergences amongst the nationally authorised products and to harmonise its divergent Product Information across Europe.
As per Article 30(2) of Directive 2001/83/EC the CMDh draws up each year a list of medicinal products intended for SmPC harmonisation. If the concerned product is included in the CMDh list the EU Commission or a Member State can start an Article 30(2) referral to harmonise the national marketing authorisations of the medicinal product [3].

Article 31 (“Union Interest Referral”)

An Article 31 referral has to be initiated by the EU Commission, the Member States, the Marketing Authorisation Holder or the applicant in case of concerns affecting the “interest of the Union” with regard to the safety, efficacy or quality of a medicinal product. This referral can include only one specific product, a range of products containing the same drug substance or a specific class of medicines involving different drug substances and products of the same therapeutic group (“class referral”) [3].

Article 107i (“Urgent Union Procedure”)

An Article 107i referral can be triggered by the EU Commission or a Member State if urgent action is needed due to safety concerns resulting from evaluated pharmacovigilance data, for example when it is considered to suspend or revoke a marketing authorisation, prohibit the supply of a drug product, refuse a renewal application or if a Marketing Authorisation Holder has stopped the market release of a drug product or has withdrawn a marketing authorisation. This procedure also applies if it is urgently required to add a new contraindication, reduce the recommended dose or restrict the indication of a drug product.
If the safety issue relates not only to a specific product but also to a range or a therapeutic class of medicines all of these products are involved in an Article 107i referral [3].

The identified concerns about the safety, efficacy or quality of one specific drug product or a class of drug products are referred to the European Medicines Agency (EMA) for scientific assessment. Safety issues are evaluated by the “Pharmacovigilance Risk Assessment Committee” (PRAC) and afterwards by the “Committee for Medicinal Products for Human Use” (CHMP) or by the “Coordination Group for Mutual Recognition and Decentralised Procedures – Human” (CMDh), if no centrally authorised drug product is included in the referral procedure. All other cases, i.e. efficacy and quality issues, are solely evaluated by the “Committee for Medicinal Products for Human Use” (CHMP). Based on the CHMP opinion or CMDh position the EU Commission adopts a decision that has to be implemented by the concerned parties (i.e. all Member States, applicants and/or Marketing Authorisation Holders) in order to achieve harmonisation across Europe.

Further details on Union referral procedures are set out in the Notice to Applicants, Volume 2A, Procedures for marketing authorisation, Chapter 3, Union Referral Procedures, December 2016 [3].

3 Regulatory requirements for harmonisation of quality dossier not part of referral procedure

3.1 Transfer of national marketing authorisations to a Mutual Recognition Procedure

In order to ensure that the harmonisation of the national marketing authorisations of a medicinal product in the EU will be further maintained after the end of the referral procedure the national licenses need to be transferred to the Mutual Recognition Procedure. The transfer has to occur between the end of the referral procedure (CHMP opinion) and the European Commission Decision. For the subsequent MRP a Reference Member State has to be chosen by the MAH.

As per CMDh recommendation (CMDh/318/2014), *"if different strengths and/or pharmaceutical forms and/or duplicates of the product are not all authorised in the chosen RMS, different RMSs will be needed to cover the entire range of strengths and forms. The different RMSs will need to co-operate in the handling of future applications, to ensure continued harmonisation of the SmPC, PL and Labelling. Alternatively, the MAH may decide to obtain MAs for all strengths, forms and duplicates of the product in one of the RMSs, by repeat-use procedures using the MAs in the other RMSs. The latter RMSs should then transfer the role of RMS to the chosen, sole, RMS, in accordance with the proposed strategy of the MAH."* [4]

So due to the variety of the different marketing authorisations in the EU the choice of the Reference Member State can be a challenge for the MAH. In this context the MAH should consider original licenses as well as multiple/duplicate licenses registered in a country according to different legal basis (e.g. Art. 8(3) application, Article 10c informed consent application, Article 10(3) hybrid application, or Article 10(4) biological application). After selecting the Reference Member State (e.g. based on the widest range of registrations) the MAH has to approach the competent national agency for seeking their acceptance to act as RMS. In case of agreement the MAH is recommended to ask for a meeting with the RMS in order to discuss the modalities for the creation of the MRP and on other post-referral regulatory activities. Prior to this meeting the MAH should provide the RMS with a list of all registrations in the EU and a list of questions considering the following topics:

- Proposal of planned MRP organisation (number and grouping of MRPs)
- Registration of additional strengths in RMS needed for MRP (feasibility of fast track registration)
- Maintaining harmonisation between duplicate licenses not registered in RMS
- Worksharing to be used for maintenance activities
- Handling of ongoing national CMC variations after submission of harmonised quality dossier
- Handling of Production Information documents in MRP dossier (e.g. submission of full set of annexes (i.e. SmPC, Package Leaflet and Labelling) combined into one file, or submission of one single SmPC, one single Package Leaflet and one Labelling text for the presentations which are grouped under the same MRP)
- Intended applicant for forthcoming MRPs (strategy on documents procurement, e.g. letter of authorisation)
- Dossier format for MRP life cycle (e.g. submission of one common cover letter and one common electronic Application Form)
- Forthcoming variation to harmonise quality dossier

3.2 Variation for harmonisation of quality dossier

3.2.1 Classification of variation

According to the “Variation Classification Guideline” [5] the application for harmonisation of Module 3, when the quality information was not covered by the scope of the referral procedure, has to be submitted as Type II variation under category B.V.b.1.b:

“B.V.b.1.b Update of the quality dossier intended to implement the outcome of a Union referral procedure
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it”

Within the framework of the harmonisation the approved quality information are aligned among the different countries. If applicable, the module 3 sections can be reformatted from old NTA format to CTD format. Other changes or updates in Module 3 not related

to the harmonisation are not acceptable during this variation procedure and have to be submitted as separate variations according to the Variation Classification Guideline.

If the same national product is registered in different countries by the same MAH the Type II variations should be submitted in a worksharing procedure.

3.2.2 Required documentation

In order to support and justify the harmonisation of the quality dossier and the pharmaceutical sections of the Summary of Product Characterisation (and related sections in the Labelling and Package Leaflet) the required documentation has to be created before submission of the variation. According to Annex IV of the Commission Regulation (EC) No 1234/2008 [6] the following supporting documentation should be submitted with the variation application for each concerned product and MRP respectively:

Module 1:

- 1.0 Cover letter
- 1.2 Electronic application form (including a list of all authorised medicinal products concerned) and annexes:
    - Copy of the relevant pages from the European Guideline for Type II B.V.b.1.b variation
    - Variation overview on pharmaceutical documentation, including a comparison of current registered and proposed situations (if not listed in the “present/proposed table” in the application form)
    - Overview tables of present and proposed English Product Information
    - Flow-chart indicating all sites involved in the manufacturing process of the medicinal product or active substance (Annex 5.8)
    - Copy of GMP certificate for each registered drug product manufacturing site(s) (including local secondary packaging sites as stated in section 3.2.P.3.1)
    - A declaration from the Qualified Person responsible for batch certification that the active substance manufacturer referred to in the marketing authorisation operates in compliance with the detailed guidelines on good manufacturing practice for starting materials

- 1.3.1 Proposed modified Product Information with the harmonised quality sections (common clean and track – PDF version): Summary of Product Characterisation (SmPC), Labelling and Package Leaflet
- 1.4.1 Information about the quality expert

It should be taken into account that the manufacturers listed in Part A of the QP declaration [7] and in Annex 5.8 are consistent with the information on drug substance manufacturers provided in section 3.2.S.2.1.

Besides these common annexes, where relevant, additional specific country annexes needs to be submitted, e.g. "proof of payment" of required national fees for the Type II variation or national cover letters. If the variation application will be submitted centralised by the corporate entity/company headquarter on behalf of the national Marketing Authorisation Holders belonging to the same company group a letter of authorisation from each Marketing Authorisation Holder to corporate entity/company headquarter to act as applicant is required. Additionally the dispatch list indicating the submission dates of the Type II variation in each CMS has to be forwarded to the RMS.

Module 2:

- 2.3.S Quality Overall Summary – Drug Substance
- 2.3.P Quality Overall Summary – Drug Product
- 2.3.A Quality Overall Summary – Appendices
- 2.3.R Quality Overall Summary – Regional Information

Module 3:

- 3.2.S Drug Substance
- 3.2.P Drug Product
- 3.2.A Appendices
- 3.2.R Regional Information

The amended quality information (Module 3) to be provided is listed in detail in Annex 1.

“Working Documents” folder:

- English Product Information (common clean and track – WORD version)
- Other specific national requirements as applicable

The national translation of the Product Information are not part of the initial submission package and have to be submitted to the national competent authorities after the end of the procedure.

3.2.3 Submission format

According to the HMA eSubmission (electronic submission) roadmap [8] the use of eCTD as submission format is mandatory for all regulatory activities in European procedures (DCP/MRP) as of 1 January 2018. This refers to all submission types for a dossier such as variations, renewals, responses to questions, etc. Once the first submission is dispatched in eCTD format all future submissions have to be submitted in the same format.

Although it is not required to submit a baseline dossier (meaning re- submission of previously submitted and approved files), the RMS could request the applicant to provide an eCTD baseline for the current approved Module 3 in the RMS before the start of the MRP.

The technical requirements for eCTD electronic submission (such as structure, file naming, bookmarks, hyperlinks, metadata) have to be met as laid down in the eCTD guidelines [9, 10].

Before the submission of the first eCTD sequence with a MRP the applicant should carefully think about the organisation and structure of the eCTD application, also with regard to the handling of future submissions and related workload. It is recommended to have one single eCTD covering all concerned Member States, strengths and dosage forms of a drug product.

A tracking table listing all submitted eCTD sequences has to be provided in Module 1 as attachment to the common cover letter with each submission sequence for MRP. The submission of the baseline dossier is considered as sequence 0000. The first variation following the transfer of the national licenses to MRP is generally the Type IA_{IN} variation to implement the Article 30 referral outcome (sequence 0001) followed by the submission of the harmonised dossier (sequence 0002).

3.2.4 Coordination and Timelines

In order to maintain the harmonisation between all the different marketing authorisations it is recommended to submit the same variation in one application through worksharing procedure combining all national marketing authorisations (original and duplicates) and MRPs concerned, respectively. For this purpose the applicant has to send a *"letter of intent for the submission of a worksharing procedure to the CMDh according to Article 20 of Commission Regulation (EC) No. 1234/2008"* [11] not less than 6 weeks in advance. As described in the "CMDh Best Practice Guide on Worksharing" [12] the following information is to be provided with the letter of intent:

- List of all authorised medicinal products to be included in the worksharing procedure
- Type, description and background of proposed change(s)
- Justification/suitability for proposed worksharing
- Target date for submission
- Selected reference authority (including explanation of its selection)
- Explanation/confirmation that all marketing authorisations concerned belong to the "same Marketing Authorisation Holder"

Based on the documentation provided, the worksharing request will be discussed in the next CMDh meeting, if possible. It should be noted that these meetings take place only once a month. Within two weeks following the CMDh meeting the MAH will be informed about the acceptance of the worksharing request, the reference authority and the worksharing procedure number.

The variation application and the corresponding documentation will be submitted by the MAH at the same time to the RMS and all concerned Member States. In general, Type II variations and worksharing procedures are processed according to a 60 days evaluation timetable as described in detail in the "CMDh Best Practice Guide for the handling of Type II Variations in the Mutual Recognition Procedure" [13] and "CMDh Best Practice Guide on Worksharing" [12].

Timetable for Type II variation/worksharing procedure (60-day procedure) [12, 13]

Day 0	Start of procedure After validation of the submitted variation application the RMS informs the CMS and the MAH about the start of the variation procedure and the timetable.
Day 40	Circulation of PVAR The RMS sends the Preliminary Variation Assessment Report (PVAR) to the CMSs for comments and to the MAH for information. The RMS recommendation on the variation application (acceptance, rejection, amendment/request for supplementary information) based on the review of the provided data is clearly indicated in the PVAR.
Day 55	CMS's comments on PVAR After receiving the PVAR, the CMSs send their comments and their opinion on the submitted variation to the RMS. If the CMSs agree with the RMS's recommendation for the acceptance or rejection of the variation, the procedure can be finalised in the first phase of the procedure and no clock stop is required. In case the proposed variation is considered as "not approvable" the CMSs can request supplementary information by the MAH.
Day 59	Request for supplementary information (RSI), clock-stop If the RMS or any of the CMS do not accept the variation in its proposed form the MAH will be requested by the RMS to provide supplementary information within a given deadline. The clock of the procedure will then be stopped.
Clock off period	In general a time frame of 120 days is scheduled for the clock-off period: The deadline for the MAH to submit the responses to the RSI is 60 days. If necessary the MAH can contact the RMS for further clarification (e.g. on proposed response strategy) during the clock-off period. Following receipt of the supplementary information by the MAH the RMS prepares the Final Variation Assessment Report (FVAR) within 60 days.
Day 60	Circulation of FVAR The procedure is restarted by the RMS with circulation of the FVAR to the CMS and the MAH.

Day 75	Break-out meeting If needed, a meeting (in form of a hearing or teleconference) can be held between all Member States and the applicant to discuss relevant items of "Potential Serious Risk to Public Health" (PSRPH) [14].
Day 80	CMS's comments on FVAR The CMSs send their comments on the FVAR and the variation to the RMS. In general no new issues should be raised by the CMS in the second phase of the procedure. The CMS should only address comments on the FVAR if the MAH has not been adequately responded to the RSI.
Day 90	End of procedure After the review of the variation is finalised the RMS will inform the CMS and the MAH on the outcome of the procedure. If the variation is accepted the RMS circulates the approval letter with the date of acceptance. In case of rejection the RMS sends the reason for refusal to the CMS and the MAH. In case of disagreement meaning that the RMS recommends an approval and at least one CMS raise a "Potential Serious Risk to Public Health" (PSRPH) the matter will be referred to CMDh.

If questions and/or comments are raised by the RMS and/or CMSs during the evaluation of the variation application the applicant has to prepare the corresponding responses within 60 days after receiving the RSI. If some of the requested information cannot be submitted within the given timeframe the applicant should make a commitment with the response that the outstanding issues will be provided until an agreed date.

The response document should be included in section "Responses to Questions" in Module 1. To be in alignment with the responses the appropriate sections in Module 3 as well as the Quality Overall Summaries in Module 2 need to be updated. Where applicable, new proposed English Product Information (SmPC, Labelling and Package Leaflet) should be provided in Module 1.3.1 (PDF versions) and the "working documents folder" (WORD version), respectively. The response documentation has to be submitted as a new eCTD sequence to the RMS and all concerned Member States [15].

In the draft Final Assessment Report (FVAR) the RMS assesses the responses and the additional documentation received from the applicant. In general the RMS also liaises with the CMSs who had raised questions to have their opinion on the draft FVAR. If the RMS considers that some of the points raised are not resolved the applicant will be requested one more time to provide supplementary information. Only after submission and review of the responses to the outstanding issues the clock will restart and the final assessment report will be circulated to all CMS. Nevertheless at that stage there will still be the possibility for any CMS to raise additional/new questions or comments that will be sent to the applicant for further clarification. Depending on the necessary round of questions the end of the procedure will be delayed accordingly.

3.2.5 Implementation

The harmonised quality dossier approved within the framework of a worksharing procedure can be implemented 30 days after the MAH has been informed about its acceptance by the RMS. In case the applicant decides to use a transitional period for implementation of the applied changes this period should be declared in the Variation Application Form.

If the pharmaceutical sections of the SmPC, Labelling or Package Leaflet has been amended due to the harmonisation of the quality dossier the national translations of the approved common (English) Product Information texts should be submitted outside the eCTD to all CMSs within 7 days after the end of the procedure considering the national requirements for electronic submission.

After approval of the translations or if no comments are received by the competent authorities within 30 days after submission of the national texts, the Labelling changes can be implemented [12].

According to Article 57(2) of Regulation (EC) No 726/2004 [16] information on the drug product authorised in the EU and the European Economic Area (EEA) has to be submitted electronically by the MAH to the European Medicines Agency (EMA). If applicable, the approved changes to the already submitted data, including the latest approved SmPCs by the Authorities, have to be submitted within 30 calendar days after obtaining approval of the variation procedure to the xEVMPD (extended EudraVigilance Medicinal Product Dictionary) [17].

4 Assessment of quality dossier with regard to potential deficiencies

In general the quality dossier contains the required chemical-pharmaceutical and biological information for active substances and finished products. However, the already approved quality documentation for medicinal products which are registered and marketed for several years (e.g. over 10 or 20 years) is usually not very detailed and might no longer comply with the current regulatory requirements. When submitting a Type II variation to harmonise the quality dossier it has to be taken into account that after review and evaluation of the variation application the provided quality documentation on drug substance and drug product might be considered insufficient and need to be adjusted according to the current requirements.

In the following a short overview is given on the information that is expected in the quality documentation of active substances and sterile finished products as laid down in various current quality guidelines. Some of the potential deficiencies in the Module 3 dossier that might be identified by the Health Authority during the review are presented.

Further information on the required information in Module 3 is described in detail in the referenced guidelines.

4.1 Drug substance

All relevant information on the drug substance is to be provided in section 3.2.S as described in the “Guideline on the chemistry of active substances” [18].

In case when a Certificate of Suitability (CEP) is referenced for the drug substance the relevant information is provided in the CEP dossier. The European Certificate of Suitability is provided in section 3.2.R.

4.1.1 General Information

Information on the identity of the drug substance, such as name/nomenclature, structural attributes (structural and molecular formula, relative molecular mass, and stereochemistry) and general characteristics (appearance, physicochemical, solid-state

and, as applicable biological properties, solubility information) should be provided in section 3.2.S.1 [18].

4.1.2 Manufacture

Manufacturer

Each manufacturer, contractor or local facilities, involved in the different steps of drug substance manufacturing has to be listed in section 3.2.S.2.1 stating their company name, address and activities (i.e. manufacturing, analytical control testing, labelling, packaging or batch release) [18].

Description of manufacturing process

The synthesis of the drug substance, including all process steps from defined starting materials to resulting intermediates and to final drug substance, has to be presented in section 3.2.S.2.2 by means of a flow diagram stating the structural formula of starting materials and intermediates with stereochemistry and chemical name. Any reagent and solvent involved in the chemical reaction or isolation should also be indicated. Additionally a detailed narrative description of the successive process steps including the amounts of all materials used, critical steps, process parameter, process controls, typical yields at each stage (taken each manufacturer into account), and maximum batch size of drug substance should be provided. If an alternative process is available it should be described in the same way as the main process. Reprocessing should also be indicated with associated method and criteria and justified by supporting data in section 3.2.S.2.5. With regard to recovered reagents and solvents (in accordance with ICH Q7 [19]) appropriate specifications have to be provided to demonstrate their suitability for reusing. In case of reworking it is not required to include the associated procedures in section 3.2.S.2.3 [18].

Control of materials

All materials required to manufacture the drug substance, e.g. raw/starting materials, reagents and solvents, etc. as cited in the process description in section 3.2.S.2.2, have to be listed for each process step in section 3.2.S.2.3, including adequate and justified specifications (tests, methods and acceptance criteria).

In case of (starting) materials derived from biological or vegetables sources information on their origin, characterisation, processing/ manufacture and quality control have to be

provided. In addition data on viral safety/risk of TSE (*transmitting animal spongiform encephalopathy agents*) (animal origin) and contaminants (plant origin) needs to be included [18].

The starting materials have to be determined according to the requirements laid down in ICH Q11 guideline [20]. Therefore, supplementary information needs to be submitted in order to justify that the selected starting material meets the criteria for defining a starting material, e.g. incorporated in the drug substance as an important structural element, commercially available, and well-defined chemical structure, characteristics, properties and impurity profile.

The manufacturer/supplier of each starting material (company/facility name and address) and a flow diagram describing the synthesis of the starting materials, including all materials used such as solvents, reagents, catalysts, has to be provided. Adequate and full specifications for the defined starting materials should be given. It is expected that appropriate limits for specified, unspecified and total impurities as well as for solvents and reagents are included in the specifications. The carryover of impurities contained in the starting material through the process steps to the drug substance needs to be also discussed. In addition specific information on the control of potential isomeric impurities should be provided. The analytical testing should be performed with validated methods [18].

With regard to solvents it should be taken into account that the contamination of some (residual) solvents (e.g. acetone, methanol, ethanol, isopropanol) with class I solvents (such as benzene) should be discussed.

Control of critical steps

In section 3.2.S.2.4 critical steps as well as intermediates controlled during the manufacturing process (as described in section 3.2.S.2.2) should be indicated along with tests, methods, acceptance criteria and a brief rationale to demonstrate that the physical and/or chemical quality of the drug substance is ensured. The specification for isolated intermediates should include the control of the potential impurities. If the analytical testing of the intermediates is performed with an internal or non-pharmacopoeial method the Health Authority could request to provide the method description. The corresponding validation data (including limit of detection, limit of quantitation and specificity) is only required if this method is strictly necessary for the control of the drug substance, e.g. in order to demonstrate that a genotoxic impurity has been removed in the course of the manufacture and is not contained in the final drug substance [18].

Process validation

Relevant validation data have to be included in section 3.2.S.2.5 if aseptic processing and/or sterilisation are performed during the manufacture of the drug substance [18]. However, for biological/biotechnological products all process validation data (including intermediate stages and full testing of the final drug substance) have to be provided to demonstrate the capability of the manufacturing process of producing the drug substance meeting the determined specification with a consistent quality.

Manufacturing process development

Information on modifications of the manufacturing process used from the beginning of development with evaluation of the changes should be given in section 3.2.S.2.6 [18].

4.1.3 Impurities

The potential impurities of the drug substance occurring during synthesis, purification and storage should be summarised in section 3.2.S.3.2, considering residual solvents, reagents (e.g. ligands, catalysts), intermediates, degradation products, elemental impurities and related substances. The origin of the impurities should be indicated and brief information on the isolation and characterisation of the synthesis impurities and degradation products should be provided. Furthermore it is expected that the carryover of each specified impurities through the process steps to the drug substance is discussed and evaluated. The analytical procedures used for determination of impurities, including relevant validation parameters (e.g. limit of detection and limit of quantitation), should also be indicated in section 3.2.S.3.2. A rationale for the inclusion or exclusion of the impurities in the specification based on the impurity profile as well as for selecting impurity limits based on safety consideration should be provided [18, 21].

According to ICH M7 (R1) [22] the identified impurities have to be also assessed with regard to its mutagenic and carcinogenic potential. Depending on the classification (Class 1-5) an acceptable limit for the intake of the mutagenic impurity has to be defined based on the risk assessment. If a mutagenic impurity has been identified an appropriate control strategy needs to be established to ensure that the level of this impurity in the active substance does not exceed the acceptable limit. Although this requirement is only applicable in case of certain post-approval changes (e.g. change in manufacturing process, controls, or composition) it should be taken into account that

the Health Authorities might request an appropriate risk assessment after the review of the proposed harmonised quality dossier.

4.1.4 Control of drug substance

The specifications for the drug substance, including at least criteria to ensure the identity, purity and content, should be listed in section 3.2.S.4.1 [23].

The analytical test procedures should be described in detail considering reagents, standards and solutions, equipment, analytical conditions and procedure, system suitability, and calculations in section 3.2.S.4.2.

The analytical procedure must be validated with regard to its specificity, linearity, detection limit, quantitation limit, range, accuracy and precision. The validation data provided in section 3.2.S.4.3 should confirm the suitability of the analytical procedure for the determination of the respective test item [18]. If alternative in-house methods are used for the control of the drug substance equivalency with the Ph. Eur. method needs to be demonstrated (“cross validation”).

Section 3.2.S.4.4 should include information about the comparability of the drug substance manufactured through the use of different starting materials/intermediates, obtained from different suppliers and using different processes, as required by the guideline EMA/CHMP/BWP/429241/2013 [24].

The justification for selection of test procedure and setting of acceptance criteria for relevant tests should be provided in section 3.2.S.4.5.

4.1.5 Reference standards

The reference standards used for the testing of the active substance should be described in section 3.2.S.5, including its specifications, characterisation (analytical and physico-chemical properties), preparation, impurities, and assay. In addition full analytical results (Certificate of Analysis) for the standards should be given, except for WHO standards or reference standards of internationally recognised pharmacopoeias (e.g. USP). The reference standards, in particular internal working standards, should be qualified and characterised against pharmacopoeial primary reference standards (Ph. Eur., BP or if justified also USP) [18].

4.1.6 Packaging

The full container closure system of the drug substance, consisting of primary and secondary packaging, should be briefly described in section 3.2.S.6, including its type of material and specifications.
The suitability of the container closure system may be discussed regarding the selected materials, protection from moisture and light, and compatibility of the packaging materials with the drug substance. In addition the conformity of the primary packaging to regulations and/or compendial requirements currently in force has to be demonstrated [18].

If the primary packaging consists of non-pharmacopoeial plastic material it is required to provide results from leachable/extractables studies and where necessary, a toxicological evaluation of the identified substances [25].

4.1.7 Stability

The assessment of the stability profile of the drug substance when stored in the primary packaging is provided in section 3.2.S.7. The stability studies conducted and the conclusion with regard to specifications, shelf life and storage directions are discussed in section 3.2.S.7.1. The stability results of the respective studies are reported in section 3.2.S.7.3 [18].

The retest period of the drug substance and the recommended storage conditions should be defined based upon:

- Stress stability testing: The stress testing should be performed under accelerated conditions (40°C ± 2°C/75% RH ± 5% RH) according to ICH Q1A (R2) to investigate the impact of heat, humidity, oxidation and hydrolysis on the stability of the drug substance and to identify the potential degradation products [26, 27].
- Photostability data: One batch of the drug substance should be exposed to artificial light according to ICH Q1B conditions to assess if the drug substance is photosensitive to light and should be stored protected from light [28].
- Primary stability studies: Three drug substance batches should be put under stability testing according to ICH Q1A conditions (long-term storage: 5°C ± 3°C, 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH, accelerated conditions: +40°C ± 2°C/75% ± 5% RH) [26, 27].

Based on the stress stability data the major pathways of drug substance degradation should be defined and discussed in section 3.2.S.3.2

4.2 Drug Product

4.2.1 Manufacturing of sterile medicinal products

All relevant information on the manufacture is to be provided in section 3.2.P.3 for finished drug products as described in the “Guideline on manufacture of the finished dosage form“ [29].

According to the “Guideline on the sterilisation of the medicinal product, active substance, excipients and primary container” [30] additional information on sterilisation procedures and aseptic processing has to be included in sections 3.2.P.2 and 3.2.P.3.

Manufacturer

Each manufacturer, including contractors or local facilities, involved in the different steps of manufacturing has to be listed in section 3.2.P.3.1 stating their company name, address and activities (i.e. manufacturing, analytical control testing, labelling, packaging or batch release) [29]. It should be considered that the current valid GMP certificate of each manufacturer should be submitted with the variation package in Module 1. These documents could be retrieved from the EudraGMDP database [31].

Batch formula

The batch sizes and the corresponding formulas of the finished drug product should be given in section 3.2.P.3.2 listing each component processed during the manufacture (including solvents, gas and any component removed from the final product), their quantities and reference to quality standard [29].

Description of manufacturing process

A brief description and a corresponding flowchart of the drug product manufacturing process, indicating all successive manufacturing steps, components/materials used for each step and relevant in-process controls carried out during the step concerned, should be presented in section 3.2.P.3.3. Moreover the type of equipment/apparatus

used, appropriate process parameter (such as time, temperature, or pH) with set points and acceptance criteria for the in-process controls should be included in the process description. The information on the manufacturing process should be validated during development and adequately justified in section 3.2.P.2.3 [29].

For sterile products the description of the sterilisation process along with the relevant operation conditions has to be included in section 3.2.P.3.3. In addition validated sterilisation conditions for primary packaging units including name and address of sterilisation sites (if outsourced) should be stated as this information is considered to be part of the manufacturing process [30].

In case of sterile filtration it is expected that the concrete type, number, material, pore size and area of the sterilisation filters (and pre-filters where appropriate) are indicated for all manufacturing sites. With regard to the required filter integrity test the used integrity test method and the concrete acceptance criteria prior and after filtration should be provided. Furthermore it should be stated how the sterile filter is sterilised and whether the filter is single-use (i.e. for one filtration only) or not. If the filter is re-used the frequency of the filter usage should be verified by data. Maximum filtration and filling durations as well as holding periods and storage conditions (e.g. for storage of pre-filtered bulk solution or from start of compounding to end of filtration) should also be mentioned according to the validation data in section 3.2.P.3.5 [30].

Prior to sterile filtration the bioburden of the bulk solution has to be tested directly prior to sterile filtration. As stated in the current EMA guideline a bioburden limit of more than 10 CFU/100 ml is not acceptable [30]. If the currently approved bioburden limit does not meet this required limit of 10 CFU/100 ml it should be taken into account that the Health Authority could request to review and update the control applied for bioburden to ensure that it adhere to EMA quality guideline.

Control of critical steps

The critical steps and product intermediates, which were determined during the development of the manufacturing process (and as indicated in the process description), along with the relevant in-process controls, acceptance criteria, methods and appropriate rationale for performing the controls should be listed in section 3.2.P.3.4 [29].

Process validation

The validation of the manufacturing process should be described in section 3.2.P.3.5. In addition validation results of at least three consecutive production scale batches verifying that the manufacturing process of the drug product is capable of consistently producing the drug product of the required quality should be presented. It is required that in particular critical manufacturing steps as described in section 3.2.P.3.3 (such as sterilisation, filling or aseptic processing) must be adequately covered by validation studies in order to demonstrate the suitability of the process/method for the intended use [32]. Therefore the following items should be addressed:

- Filtration process of bulk product solution, including maximum filtration durations, holding times with storage conditions and filter properties (bacterial retention capacity, chemical compatibility, and potential extractables/leachables)
- Filling process including maximum filling time
- Sterilisation and depyrogenation processes used for containers, closures, equipment and components, considering the required data laid down in the respective guidelines and /or ISO norms (e.g. ionisation radiation sterilisation: ISO 11137 [33], gas sterilisation: ISO 11135 [34])
- Container closure and package integrity (microbial integrity of the container closure system)

In case of standard sterilisation processes (such as dry heat or steam sterilisation) performed according to Ph. Eur. validation data is not required. If the conditions of the referenced Ph. Eur. methods are not met during the sterilisation cycles adequate validation (physical/biological data) has to be provided to demonstrate a sterility assurance level of 10^{-6} (or better) [30].

4.2.2 Excipients

The excipients that are contained in a sterile medicinal product have to be listed in section 3.2.P.1 including their amount (per unit or percentage), their function and a reference to pharmacopoeial or in-house monograph used as quality standard. The selection of the excipients, their quantity, the effect of the excipient on the drug product characteristics and the compatibility between the excipients and with the active ingredient should be discussed in detail in section 3.2.P.2. With regard to section

3.2.P.4.1 it is expected that adequate limits for bioburden and endotoxins are included in the specification of the excipients.
If an antioxidant or an antimicrobial preservative is included in the drug product formulation the use and the effective concentration of these substances need to be adequately explained and justified in section 3.2.P.2.2. Although the testing for preservative content is usually included in the drug product specifications, antimicrobial preservative effectiveness should be demonstrated during pharmaceutical development, shelf life and in-use conditions (according to the pharmacopoeias) [35].

4.2.3 Control of drug product

Specifications and analytical methods

All applicable specification tests and acceptance criteria for batch release (and shelf life) including reference to pharmacopoeias must be listed in section 3.2.P.5.1. The testing parameters relevant with regard to the dosage form should be included in the specifications in compliance with the corresponding Ph. Eur. monograph (e.g. for parenteral preparation) and further ICH Q6A, Ph. Eur. requirements, respectively [23].

The analytical test procedures have to be sufficiently described (including reagents, standards and solutions, equipment, analytical conditions and procedure and calculations) in section 3.2.P.5.2 if non-compendial methods are used. Alternative methods according to USP and JP as referenced in the ICH Q4B Annexes are accepted as they are considered as interchangeable [36].

The analytical procedures need to be validated according to ICH Q2 (R1) [37]. The results obtained at validation with regard to accuracy, precision, specificity, detection and quantitation limit, linearity and validity range should demonstrate that the method is suitable for the determination of the test parameter. It is expected that the test for microbial contamination and sterility has been validated according to Ph. Eur. or alternatively that adequate validation data are provided. The documentation on method validation is provided in section 3.2.P.5.3.

For each test a brief rationale for the selection of analytical method and a justification for the acceptance criteria should be given in section 3.2.P.5.6.

Impurities

The impurities existing in the drug product should be summarised in section 3.2.P.5.5. In this summary all impurities originating from the synthesis/manufacture or occurring during storage (such as starting materials, reagents, catalysts, heavy metals, intermediates, residual solvents and degradation products) should be discussed. The origin of the impurities as well as the degradation pathway should also be indicated. The investigations with regard to identification/characterisation, quantification and qualification of the individual impurities are performed according to the current ICH guidelines.

It should be taken into account that the “ICH guideline Q3D on elemental impurities” applies not only to new registration applications but it is also effective for existing authorised drug products including new MRP procedures of already authorised products since December 2017 [38]. So this issue could be raised during the review of the proposed harmonised Module 3. In order to implement the ICH Q3D guideline for authorised/marketed products a risk assessment should be conducted to evaluate the level of elemental impurities in the drug product and to define the level of control and the required additional actions to ensure that the permitted daily exposure (PDE) of each element is not exceeded in the drug product. The risk assessment should consider the 24 elemental impurities as classified in the guideline based on their toxicity and probability of occurrence in the drug product, the route of drug product administration and the PDE level of each element depending on the route of administration. The identification of potential elemental impurities in the drug product could be performed according to the following approaches:

- Medicinal product approach: This approach is based on the assessment of potential elemental impurities directly in the medicinal product
- Component approach: This approach is based on the review of all potential sources of elemental impurities in the components and associated processes used in the production of the drug product (drug substance, excipients, manufacturing equipment, facilities/utilities (water/air) and container closure system).

According to the outcome of the risk assessment an appropriate testing control strategy needs to be defined for the drug product:

- If elemental impurities are not likely to be present or are below the defined control threshold of 30% of PDE, no further action is required and the existing controls performed could be considered as sufficient.
- If the elemental impurities level is greater than the control threshold (30% of PDE) or in worst case greater than the PDE, the source of the impurity should be identified to reduce its content and a limit/specification should be established to control the level of the identified elemental impurity in the drug product or component.

The evaluation of the elemental impurities (i.e. the risk assessment) is summarised and documented on the drug product manufacturing site and has to be available during an inspection. In Module 3 the summary of risk assessment report should be provided in section 3.2.P.5.5 [38].

During life cycle management it should be considered that a re-evaluation of the risk assessment and the control strategy is necessary if any change has a potential impact on the elemental impurity level in the drug product.

4.2.4 Reference standards

The reference standards used for the testing of the drug product should be described in section 3.2.P.6, including its intended use, origin, specifications, characterisation (analytical and physico-chemical properties), preparation, impurities, and assay. In addition full analytical results (Certificate of Analysis) for the standards should be given, except for WHO standards or reference standards of internationally recognised pharmacopoeias (e.g. USP). The reference standards, in particular internal working standards, should be qualified and characterised against pharmacopoeial primary reference standards (Ph. Eur., BP or if justified also USP).

4.2.5 Packaging

Relevant documentation on the primary packaging (i.e. type of container and closure) for the drug product is to be provided in sections 3.2.P.2.4 and 3.2.P.7.

In section 3.2.P.2.4 a brief description of the container closure for drug product should be given. The studies that led to its selection and confirm its suitability have to be discussed considering the following items:

- Rationale for selection of packaging materials (e.g. compliance with compendial requirements)
- Suitability concerning protection from light/moisture
- Compatibility of drug product with all components of primary packaging in contact with the drug product solution
- Sorption of the container (adsorption/absorption of drug product components to packaging material)
- Leachables/extractables
- When relevant, demonstration of functionality (e.g. for pre-filled syringes) and/or performance (e.g. reproducibility of the administrated dose from multidose delivery device)

For sterile liquids extractables studies are required in particular for primary packaging components made of non-pharmacopoeial plastic materials. These studies are not requested for glass containers. Solvent extractable studies have to be performed with various aqueous and organic solvents under stress conditions to allow the determination of the qualitative extractable profile of any part of primary packaging in contact solution. Based on the results of these studies the leachables from the drug product solution filled in primary packaging has to be determined. Leachables might be confirmed through shelf life results by determination of extractables at shelf life to support the leachable assessment. If leachables/extractables are present in the drug product solution a toxicological evaluation of these substances is required to determine if the level of exposure is of toxicological concern or not [25].

In section 3.2.P.7 each packaging component has to be described in detail, including its material type, its specifications (with reference to the appropriate compendial method or in-house monograph and corresponding compliance statement) and analytical procedures used to control the packaging materials. The technical drawings as well as the critical dimensions of the primary packaging should also be given.
If plastic materials are used for the primary packaging the identity testing should be included in the material specification. In case of a non-solid dosage form (i.e. inhalation, ophthalmic or parenteral products) the supplier and the qualitative composition of each

plastic material need to be listed [25]. For the sake of completeness a description of the secondary packaging should also be included in section 3.2.P.7.

For liquid sterile pharmaceutical forms it is also expected that the capability of the container closure system to maintain sterility and to prevent any microbial contamination is demonstrated. The integrity of the container closure system should be confirmed by visual inspection at the end of the manufacture, microbiological challenge tests and/or dye intrusion tests performed at release/during stability studies.

4.2.6 Stability

The assessment of the stability profile of the drug product when stored in the primary packaging intended for commercial use is provided in section 3.2.P.8. The stability studies conducted and the conclusion with regard to specifications, shelf life and storage directions are discussed in section 3.2.P.8.1. The stability results of the respective studies are reported in section 3.2.P.8.3.

The shelf life of the drug product and the recommended storage conditions should be defined based upon:

- Photostability data: One batch of the drug product should be exposed to artificial light according to ICH Q1B conditions to assess if the drug product is photosensitive to light and should be stored protected from light [28].
- Primary stability studies: Three drug product batches should be put under stability testing according to ICH Q1A conditions (long-term storage: 5°C ± 3°C, 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH, accelerated conditions: +40°C ± 2°C/75% ± 5% RH) [26, 27].
- In-use stability studies: In order to investigate administration conditions of a drug product in multidose container (e.g. vial) an in-use stability study, simulating the dispensation of the drug product to the patient, should be performed with two batches. The stability data should confirm the recommended in-use storage time and conditions once the container is opened/punctured. It must be taken into account that batches at the beginning of shelf life as well as close to the end of shelf life have to be challenged [39]. Usually Health Authorities expect microbial results from in-use stability studies. However in some cases supportive arguments might be provided to justify an omission of sterility testing in the stability protocol. For example, there is no concern for the microbial safety of a

drug product if a multidose container must contain an antimicrobial preservative to ensure that no microbial growth occurs during the in-use period.

If a drug product needs to be diluted, mixed, reconstituted or co-administered before administration appropriate compatibility studies with different solvents or other products should be performed to provide adequate information on incompatibilities and to support the compatibility claims in the Labelling. In particular drug products intended for intravenous administration should be tested for their physico-chemical compatibility and stability with commonly used i.v. dilution solutions (such as 5% dextrose/glucose in water or 0.9 % sodium chloride solution) and delivery devices (such as infusion bags, infusion sets with or without on-line filters, infusion tubings). The results of these studies including in-use storage time and conditions should be described in section 3.2.P.2.6.

- Temperature cycling stability studies: The objective of the temperature cycling studies is to assess the impact of successive freeze and thaw cycles on the product (e.g. 3 days at - 20°C followed by 4 days at +30°C/65% RH, repeated 3 times) and thus to evaluate the stability of the drug product under adverse shipping conditions with temperature fluctuation.

For all types of stability studies reference must be made to the analytical procedures used to perform the studies which are usually described in section 3.2.P.5.2 or alternatively in section 3.2.P.8.3 for test items performed only for stability testing.

The stability studies should comprise the investigations on the chemical, physical and microbiological properties, and if applicable, on the preservative effectiveness and functionality tests of the medicinal product during the shelf life. The stability relevant test items should be performed according to the analytical procedures given in section 3.2.P.5.2.

4.3 Product Information/Labelling

As described in the “Guideline on Summary of Products Characteristics” relevant quality information has to be included in sections 2, 3, 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6 of the Summary of Product Characteristics (SmPC) and the corresponding sections in the Package Leaflet as well as in the Labelling (outer packaging) [40].

In addition to the description of the strength, the dosage form, the appearance and the composition of the drug product (including all excipients) further pharmaceutical information has to be stated in the SmPC in compliance with the data provided in Module 3.

Relevant parameter that has to be considered for the administration of the drug product, such as pH and osmolality for parenteral formulations, should be summarised in SmPC section 3.

In case of co-administration or mixture of drug products, in particular in case of reconstitution/dilution of parenteral products, statements regarding incompatibilities should be included in SmPC section 6.2. According to the results of compatibility studies discussed in CTD section 3.2.P.2.6 further information on the compatibility with other products, dilution solutions or delivery devices can be stated in SmPC section 6.6.

Based on the stability study results presented in CTD section 3.2.P.8.3 the shelf life and the recommended storage condition for the finished drug product has to be clearly stated in SmPC section 6.3 [41]. If the drug product is supplied in a multidose container the maximum storage time and the temperature conditions once the container is opened/punctured or after the drug product is diluted/reconstituted should also be specified [42].

It should be taken into account that specific storage restrictions with regard to different temperature conditions (refrigerating, freezing, controlled temperature) or sensitivity to light/ moisture given in SmPC section 6.4 should be justified by corresponding stability data. A storage condition should not be added in the Labelling to compensate inadequate or missing stability studies at specific testing conditions. If the appropriateness of the additional statement has not been adequately demonstrated by the applicant the Health Authority could require further justification and data.

In SmPC section 6.5 each component of the primary packaging stating its material type should be listed as described in CTD section 3.2.P.7.

As the quality information in the SmPC, PL and Labelling is not harmonised within the Article 30 referral it should be considered that changes to standard texts in accordance with the current guidelines (e.g. “Guideline on maximum shelf life for sterile products for human use after first opening or following reconstitution CPMP/QWP/159/96 corr”) could be requested by the Health Authority [42].

5 Handling of quality dossier harmonisation in a company

The harmonisation of a quality dossier not part of a referral procedure needs to be strategically and effectively planned with regard to required activities and available resources (including timing, finances, staff/subject matter experts, equipment) in a company. In order to submit the harmonised quality dossier as soon as possible after the end of the referral procedure the MAH is recommended to start the planning and preparation of the Type II variation already during the on-going referral procedure.

As many different departments and functions are involved in this regulatory process (e.g. global regulatory affairs, local affiliates, quality control, quality assurance, production, CMC team, Labeling team, supply chain, external suppliers, different manufacturing sites) a transparent communication is essential at any time. All tasks, responsibilities and timelines have to be clearly defined.

Any regulatory sub-activity in the variation process should be tracked in the registration database of the company for transparency and documentation purposes (“end-to-end variation process”).

In order to manage all changes related to the harmonisation of the quality dossier a change request should be initiated in an adequate electronic change control system.

5.1 Pre-submission activities

Before the submission of the Type II variation B.V.b.1.b an assessment of the current regulatory situation has to be performed by identifying the affected marketing authorisations in the EU countries and evaluating the registered quality documentation. Moreover the current existing regulations, guidelines and “Best Practice Guidances” as well as the relevant homepages of the authorities (e.g. EMA, HMA, or national authorities) need to be reviewed in order to verify the required documentation.

When compiling the required documentation for the harmonisation of the quality dossier between the countries it should be taken into account that it may take some time to prepare the administrative documents and to update the Module 3 documents and Product Information texts accordingly. In particular the detailed listing of the “present/proposed” situation with regard to Module 3 sections for each country is very time consuming. In order to ensure that all mandatory documents and information are

included in the variation application a survey on the country-specific requirements should be performed.

Depending on the number of marketing authorisations and their different registration status the company should consider the possibility of using a worksharing procedure as described in section 3.2.4 “Coordination and Timelines”. When requesting for a worksharing it has to keep in mind that the submission of the variation is only possible on a monthly basis.

For the preparation of the eCTD submission all documents should be available and approved in an electronic Document Management System. If an eCTD baseline is requested by the RMS before the submission of the post-referral variations the additional workload and time for compiling and publishing of the initial eCTD sequence has to be taken into account.

In case that further clarification is needed on certain regulatory issues (e.g. with regard to the transfer of national MAs to MRP or additional requirements that needs to be considered) a meeting with the RMS should be requested.

It should be considered that enough time is scheduled for any of the required pre-submission activities.

5.2 Submission activities

According to the internally agreed submission strategy and timelines the variation package is submitted in parallel to the RMS and all CMS either by the local affiliates (national MAHs) or centralised by the company headquarter. The start of the procedure and the timetable should be communicated to all relevant functions/departments involved in the variation process.

By means of the agreed procedure timetable the applicant/company can ensure the availability of the relevant subject matter experts in case of questions by the Health Authorities. However, the company should develop an internal action plan and a corresponding time schedule in order to coordinate all required activities for preparing the responses to the RSI in the given deadline. The additional time for the internal review and approval of the response documentation as well as for the creation and publishing of the new eCTD submission sequence has to be also taken into account.

When receiving the PVAR by the RMS at Day 40 it is strongly recommended to start preparing the responses and the requested documentation. Depending on the complexity of the requests an adequate response strategy has to be discussed and agreed internally with all involved functions and, if necessary, also with the RMS.
If additional studies are required to provide the requested data it is necessary to examine whether the investigations can be performed inside the company or must be outsourced. If needed, the applicant commits to provide the additional data when available. Nevertheless, the associated costs of those studies should be considered in the budget planning of the company.

The dates and the dossier identification number of the initial as well as of the subsequent submissions (responses to questions, communication to Health Authorities) within the variation process should be entered in the regulatory database.

5.3 Post-approval activities

The approval of the variation/worksharing procedure causes some subsequent activities in the company.

The registration database of the company needs to be updated with the relevant information to reflect the current registration status in the concerned countries.
All relevant functions and departments in the company should be informed about the approval of the harmonised dossier in order to implement the related changes. After submission and approval of the national translations of the proposed SmPC, Labelling and Package Leaflet the artwork creation can be initiated.

Depending on the additional data requested by the Health Authorities within the framework of the variation procedure the identified follow-up measures should be addressed in the ongoing life-cycle of the medicinal products and tracked accordingly with the available tools in the company.

5.4 Impact on other markets/international countries

The harmonisation of the quality dossier across the European countries might have an impact on the registration in international countries if these countries refer to a marketing authorisation in the EU (i.e. the concerned EU country is the reference

country). In any case an evaluation is needed comparing the level of details included in the approved harmonised EU dossier with the international dossiers and the requirements as stated in their current regulations.

If the requested update of the Module 3 sections has no impact on the international registrations then no regulatory action is required. In case of alignment of the international registrations with the EU dossier, impacting the Labelling (SmPC, Package Leaflet and outer packaging) as well, an adequate submission strategy has to be defined. In accordance with the regulations in the international countries and the required details in the quality dossier it might be possible to submit only a grouping of some key changes. Nevertheless, in order to simplify the dossier management in all countries the preferred option should be the alignment of all changes registered in the EU dossier.

Depending on the requested changes in the EU dossier it should be considered that in some cases difficulties might arise to manage the different sets of registered data (e.g. in case of specifications, process parameters, holding times, etc.).

5.5 Subsequent regulatory activities

Due to the transfer of the national marketing authorisations to Mutual Recognition Procedure all subsequent regulatory activities (e.g. variations) have to be submitted via MRP in the RMS and all CMSs, even if the change affects only one country (e.g. administrative changes, or changes in local secondary packaging sites).

As the national marketing authorisations in the concerned Member States were granted at different times they have different renewal dates. Therefore the RMS set a common renewal date as agreed with the applicant after the end of the referral procedure. If any of the marketing authorisations is not valid for an unlimited period it should be considered that a further renewal is required according to Article 24 of Directive 2001/83/EC [1]. In this case a “shortened renewal procedure” is possible in agreement with all CMS as laid down in the “CMDh Best Practice Guide on the processing of renewals in the Mutual Recognition and Decentralised Procedures” [43]. For this administrative renewal only a reduced documentation (i.e. cover letter, application form without annexes and declaration about availability of full documentation in case of requested submission) is required and shortened timetable applies (30 days instead of 60/90 days).

6 Discussion and Conclusion

The harmonisation of the quality dossier after a Union referral procedure requires a defined regulatory strategy and time planning with regard to the activities needed prior and after the submission of the Type II variation B.V.b.1.b.

With regard to the transfer of the national marketing authorisations to a Mutual Recognition Procedure, the choice of RMS is a particular challenge for the applicant. Depending on the number of the concerned national marketing authorisations and their registration status (legal basis) and considering different pharmaceutical forms and/or strengths of a medicinal product there may be several options to group the presentations/licenses under same or different MRPs. The applicant should carefully think about the number and groupings of MRPs in particular regarding its suitability and future variation handling aspects. In any case the planned MRP organisation for the entire range of the registered drug product licenses should be discussed in detail with the chosen RMS to obtain its approval.

In parallel to these strategic considerations the applicant should already start preparing the Type II variation. For the submission of the variation package the applicant has to take into account the relevant regulatory and technical requirements as laid down in the various regulations and guidelines as well as the additional time needed for some of the pre-submission activities (e.g. worksharing request, eCTD baseline creation).

The assessment of the submitted and already approved Module 3 by the Health Authorities on the basis of current, new and updated quality guidelines means a full re-evaluation of the existing quality documentation and leads to an updated quality dossier reflecting the “current state of scientific knowledge”. This re-evaluation also has an impact on the maintenance activities of the national marketing authorisations.

Due to more stringent and increased requirements more details on the manufacture, control, impurities or packaging of the drug substance and drug product are expected in the quality documentation. As the requested level of detail is usually not included in the quality dossier of a medicinal product which is already registered for several years it is very likely that the Health Authorities request the applicant for further information.
Moreover, the applicant could also be requested to include the missing information and/or corresponding data in the appropriate Module 3 sections. In general all relevant validation data should be available at GMP level so that the dossier sections can be updated accordingly within the framework of the response documentation. In worst case additional studies have to be performed to provide the requested data (e.g. extractable

and leachables studies, filter validation studies). In any case the information request by the Health Authorities is associated with additional workload and related follow-up measures for the applicant.

The requested update of the currently approved Module 3 sections with more detailed information might result in an increase of CMC variations. Depending on the “new” level of detail in Module 3 the applicant has to submit more variations and wait for the approval before the implementation of CMC changes. These restrictions have to be taken into account during the life-cycle management of the medicinal product, in particular with regard to those changes which could be directly implemented in the past without any variation application.

As another consequence of the Type II variation B.V.b.1.b only one common harmonised dossier is applicable for all concerned marketing authorisations in the EU which simplifies the handling and implementation of future submissions. In case of any change the applicant needs to create only one variation package for all EU countries. As the variation package is submitted through MRP the applicant will receive one common variation assessment report including the opinion of all countries at the same time. The preparation of only one documentation and, where appropriate, only one consolidated response document leads to a lower workload for the involved functions in terms of maintenance activities. Moreover after common approval of the variation application the CMC change can be implemented simultaneously in all EU countries.

The harmonisation of the quality dossier after a Union referral procedure poses many challenges for the applicant/company and is associated with a heavy workload for all involved functions as many different points are to be considered with regard to the regulatory activities required before and after submission of the Type II variation.

Nevertheless the applicant/company benefits from the harmonisation procedure particularly with regard to the life-cycle management of the medicinal product. The required transfer of the concerned national marketing authorisations to MRP leads to a simultaneous submission of variations to all Member States and a common evaluation of the provided documentation by the national competent Health Authorities. In this way it is ensured that also the quality dossier remains consistent and identical in all EU countries where the drug product is registered. This means that the applicant has to manage only one dossier (Modules 2-5) within the maintenance activities of the medicinal product in the EU.

Due to the increased pharmacovigilance requirements and the divergent national decisions on the use of a drug product in the EU it can be assumed that more referral procedures will be initiated due to safety and/or efficacy issues in order to harmonise the Product Information. Moreover the yearly list of medicinal products by the CMDh according to Article 30(2) of Directive 2001/83/EC [1] also promotes the SmPC harmonization across the EU.

The initiation of more referral procedures implies that also more and more quality dossiers have to undergo harmonisation process in the EU. This in particular applies to “old” drug products which are registered and marketed over 10 or 20 years.

7 References

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf [Accessed: 30 June 2018]

[2] Guideline on the definition of a Potential Serious Risk to Public Health in the context of Article 29(1) and (2) of Directive 2001/83/EC – March 2006 (2006/C 133/05)
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/com_2006_133/com_2006_133_en.pdf [Accessed: 30 June 2018]

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8 Annexes

8.1 Annex 1: Amended Module 3 sections

Amended Quality Information (CTD Format, Module 3)	
3.2.	**BODY OF DATA**
3.2.S	**DRUG SUBSTANCE**
3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties
3.2.S.2	Manufacture
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of manufacturing process and process controls
3.2.S.2.3	Control of materials
3.2.S.2.4	Controls of critical steps and intermediates
3.2.S.2.5	Process validation and/or evaluation
3.2.S.2.6	Manufacturing process development
3.2.S.3	Characterisation
3.2.S.3.1	Elucidation of structure and other characteristics
3.2.S.3.2	Impurities
3.2.S.4	Control of drug substance
3.2.S.4.1	Specification
3.2.S.4.2	Analytical procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	Reference standards or materials
3.2.S.6	Container closure system
3.2.S.7	Stability
3.2.S.7.1	Stability summary and conclusions
3.2.S.7.2	Post-approval stability protocol and stability commitment
3.2.S.7.3	Stability data

Amended Quality Information (CTD Format, Module 3)	
3.2.P	**DRUG PRODUCT**
3.2.P.1	Description and composition of the drug product
3.2.P.2	Pharmaceutical development
3.2.P.3	Manufacture
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch formula
3.2.P.3.3	Description of manufacturing process and process controls
3.2.P.3.4	Controls of critical steps and intermediates
3.2.P.3.5	Process validation and / or evaluation
3.2.P.4	Control of excipients
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical procedures
3.2.P.4.3	Validation of analytical procedures
3.2.P.4.4	Justification of specifications
3.2.P.4.6	Novel Excipients
3.2.P.5	Control of drug product
3.2.P.5.1	Specification(s)
3.2.P.5.2	Analytical procedures
3.2.P.5.3	Validation of analytical procedures
3.2.P.5.4	Batch analyses
3.2.P.5.5	Characterisation of impurities
3.2.P.5.6	Justification of specification(s)
3.2.P.6	Reference standards or materials
3.2.P.7	Container closure system
3.2.P.8	Stability
3.2.P.8.1	Stability summary and conclusions
3.2.P.8.2	Post approval stability protocol and stability commitment
3.2.P.8.3	Stability data
3.2.A	**APPENDICES**
3.2.A.2	Adventitious agents safety evaluation
3.2.R	**REGIONAL INFORMATION**

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Ort, Datum

Unterschrift