Harmonisation of the Quality Dossier by Means of the Worksharing Procedure: A Look at Execution and Advocacy from Applicant's Perspective

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Abbreviations

API	Active Pharmaceutical Ingredient
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BPI	Bundesverband der Pharmazeutischen Industrie e.V. (German Pharmaceutical Industry Association)
CAP	Centrally Authorised Product
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CESP	Central European Submission Portal
CHMP	Committee for Medicinal Products for Human Use
CL	Cover Letter
CMC	Chemistry, Manufacturing and Controls
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CMS	Concerned Member State
CP	Centralised Procedure
CTD	Common Technical Document
DC	Decentralised
DCP	Decentralised Procedure
DE	Deutschland (Germany)
eAF	electronic Application Form
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
EoP	End of Procedure
FVAR	Final Variation Assessment Report
HA	Health Authority
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MA	Marketing Authorisation
Mfg	Manufacturing
MR	Mutual Recognition
MRP	Mutual Recognition Procedure
MS	Member State
NAP	Nationally Authorised Product

NCA	National Competent Authority
NP	(Purely) National Procedure
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PIL	Patient Information Leaflet
PoP	Proof of Payment
PSRPH	Potential Serious Risk to Public Health
PVAR	Preliminary Variation Assessment Report
QC	Quality Control
QOS	Quality Overall Summary
RMS	Reference Member State
RSI	Request for Supplementary Information
SmPC	Summary of Product Characteristics
WS	Worksharing

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1 Introduction

1.1 Initial Situation and Goal of Thesis

Drug regulatory affairs is without doubt an indispensable field in the pharmaceutical industry and inseparable from the authorisation of new medicinal products and the maintenance of established products.

Within the regulatory landscape worksharing is still rather young among procedures. Marketing authorisation procedures are evidently very important for the emergence and approval of new medicinal products. However, also methods to make changes to the regulatory documentation – commonly named variations – can be considered equally crucial. One method to submit and handle single variations or groupings of variations is the worksharing procedure.

The word “worksharing” consists of “work” and “sharing”. “Work” can be understood as assessment by a scientist or an assessor of an authority and “sharing” can be seen as division of labour, i.e. sharing the work with other competent authorities. [1]

Worksharing has been around since the beginning of 2010. For nationally authorised products the procedure is possible for applications submitted as of 4 August 2013. Since then, also harmonisations of the quality dossier – Module 3 of the Common Technical Document (CTD) – were made possible. [2] [3]

The purpose of Module 3 harmonisations is to align the quality dossier of the same products authorised through national, MR or DC procedures in different Member States of the EU. It has become more important over time as scientific standards and knowledge have changed. The worksharing procedure provides the means to achieve a harmonised outcome. [4]

Looking at the statistics one can acknowledge that numbers of started and finalised worksharing procedures have generally risen over the past 10 years, although there is still room for improvement. This view is also shared by representatives of NCAs and *Medicines for Europe*:

Question to Industry: Why is worksharing still not used more often?

Could it [WS] be used more frequently?

[5] [6]

The reasons for the lack of applications is unknown. Is it due to obstacles before or during the procedure? Perhaps there is an absence of a need to harmonise (national) authorisations? Or are the procedures just not familiar enough? This thesis aims to find out those reasons and provide a conclusion at the end to summarise the advantages and difficulties.

It also aims to provide guidance on the legal and regulatory backgrounds of worksharing and Module 3 harmonisation, the activities around the execution and the execution of the method itself and an assessment on past experiences with worksharing in general and Module 3 harmonisation in particular, as well as determine the overall advocacy along with possible improvements to the procedure.

The thesis will only cover human medicinal products and primarily the situation in the European Union. It only focuses on the voluntary type of Module 3 harmonisation and not on the mandatory form after Union referral. Referrals are used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine.

The information in the thesis is based on own experience in the field of drug regulatory affairs in the pharmaceutical industry, on the results gathered from a questionnaire specifically created within this framework, as well as on sources stated at the end of the document.

1.2 Structure of Thesis

Apart from the introduction, there are six main parts to the thesis, which are further divided into more specific sections.

Parts 2, 3 and 4 of the document focus on the legal and regulatory background of worksharing, the significance and contents of Module 3 of the product dossier and the core subject of the thesis, which is the consolidation of the quality dossier. These parts are meant to present the relevant legislation as well as insight into the proper guidelines.

The harmonisation part of the thesis includes the legal background, the decision-making process, the pre-submission activities, the execution of the procedure itself and the post-approval period. It serves to introduce the preparation for a Module 3 alignment, the specific steps applicants pass through

before and during the procedure and activities they to perform after approval on European and national level.

Parts 5 and 6 of the thesis focus on concrete worksharing experiences by the pharmaceutical industry. In order to ascertain this information, an online questionnaire was created and presented to different companies that are either headquartered in Germany or have an affiliate there.

The survey focuses on the number of worksharing procedures conducted in the past, the advantages and difficulties encountered during and before the procedure, the overall impression of worksharing and suggestions for improvement.

The survey also addresses past encounters of the companies regarding the subject of Module 3 harmonisation, as well as their advocacy on the matter.

After the questionnaire the answers are evaluated graphically and compared by company size as well as other characteristics in order to paint a picture of the different experiences. Other important points to consider are further reviewed and a conclusion is given at the end in part 7.

2 What Is Worksharing?

2.1 Background

2.1.1 Legal Basis

The definition for worksharing can be found in article 20 of *Commission Regulation (EC) No 1234/2008*, as amended by *Commission Regulation (EU) No 712/2012*, often referred to as the *Variation Regulation*:

In order to avoid duplication of work in the evaluation of variations to the terms of several marketing authorisations, a worksharing procedure should be established under which one authority, chosen amongst the competent authorities of the Member States and the Agency, should examine the variation on behalf of the other concerned authorities. [2] [7]

Member States refer to the Member States of the European Union and the *Agency* refers to the European Medicines Agency (EMA).

Article 20 sets-out the possibility for a marketing authorisation holder to submit the same Type IB or Type II variation or the same group of variations affecting more than one marketing authorisations from the same holder in one application. [8]

Worksharing is possible since the coming into effect of the *Variation Regulation*, which was January 1st, 2010. [2]

The Regulation is applicable to nationally authorised products (NAPs) as well as to centrally authorised products (CAPs). There are certain changes, however, that cannot be described by the *Variation Regulation* and follow national legislation instead, for example, change of a manufacturing authorisation holder or purely editorial changes to the product information of a medicinal product.

Worksharing is feasible for several MAs owned by the same holder. However, as there are different definitions of MAs in different Member States, sometimes that may include one strength or more than one strength of the same medicinal product. For a worksharing, at least two Member States have to be involved.

Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) has agreed that the marketing authorisation is defined through the procedure (MR-)number, e.g. *DE/H/1000/001-010*. [1]

2.1.2 Variations

The basis for any worksharing is at least one variation. Any amendment to the regulatory documentation triggers a variation. If there is a change that does not alter the regulatory information, i.e. the information in the dossier, no variation is needed. An amendment can be the addition, deletion or change of a document. [9]

Variations are categorised into Types IA, IB, II and extension applications.

Type IA variations require no assessment by an authority and are only validated. They are regarded as “do and tell” changes, which means that the change can and has to be performed before the actual approval and the relevant authority doesn’t need to be informed until after implementation, e.g. through an annual report. The annual report is a grouped application including all IA variations from the previous 12 months and can be filed at any time, but not later than 12 months after the implementation date of the first change. There is an exception, however, which is Type IA_{IN}. This type of change requires an immediate notification to the authorities. It can also be included in the annual report but would then trigger the submission of the report immediately. An example of a Type IA_{IN} would be an address change of a manufacturer. The procedure lasts 30 days.

Type IB variations are usually categorised “by default”. This means that if the variation can neither be classified as Type IA nor Type II, it is automatically classified as Type IB. The procedure lasts 30 days with the possibility of a clock stop (pausing the procedural *clock*) and an additional 30 days of assessment. A validation phase of 7 days is due prior to the start of the procedure. Before the planned changes can be implemented, approval by an authority is needed. If no official approval is issued there is the possibility of an implicit approval (see also section 4.6).

The procedures for Type II variations usually require a lot more time and assessment. They are commonly applicable if there are major changes to the product’s documentation, like a change to the indication or a more extensive change to the manufacturing process. In order to be able to implement the changes, prior approval is also required. The procedure can take 30, 60 or 90

days, depending on the type of change, with the possibility of a clock-stop. The 60-day procedure is the standard operation.

Extension applications (or *line extensions*) are an exceptional type that concern more severe changes to a marketing authorisation, like changes to the strength, the pharmaceutical form or the route of administration. It is usually approved according to the same procedure as for a new MA and follows the same timeline. It is defined in Annex I of the *Variation Regulation*. [2] [9]

Variations are classified by means of a risk-based approach (Figure 1). The higher the level of risk, the higher the classification. The higher the classification, the longer the assessment and (usually) the greater the fees. The level of risk can be understood as the extent of impact on the quality, safety and efficacy of a medicinal product.

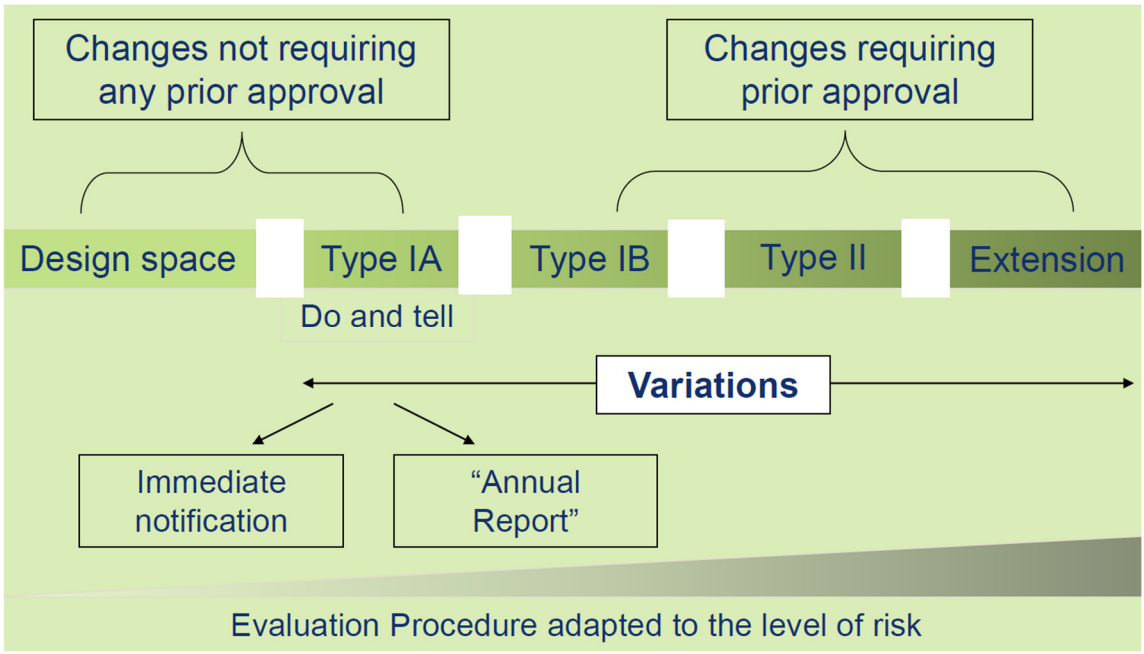

Figure 1 Classification of Variations

[9, p. 204]

The tool for the correct classification of variations is the *Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products* of the European Commission, often just referred to as the *Classification Guideline*. [10]

2.1.3 Groupings

According to article 7.1 of *Commission Regulation (EC) 1234/2008*, each variation requires one notification to the relevant authority. Under certain circumstances, according to article 7.2 of this Regulation, the applicant may deviate from the aforementioned process and several variations may be grouped into a single notification.

Possible cases for groupings are listed in Annex III of the Regulation. Any other groupings have to be justified and the relevant authority has to agree to subject those variations to the same procedure. For products authorised via MRP or DCP, the CMDh also features examples for acceptable groupings. [2] [11]

Type IA variations can always be grouped, e.g. within an annual report (unless other types of variations are included). It can also include a Type IA$_{IN}$, but the Type IA$_{IN}$ would need to be submitted immediately. Unlike other types, for Type IA it is also possible to group changes for more than one marketing authorisation (but for the same MAH).

Other possibilities for groupings are an extension application with associated variations, a Type II with consequential changes, a Type IB with consequential minor variations, administrative changes to the SmPC, PIL and labelling etc., as described in Annex III of the Variation Regulation. [2]

The timetable for the procedure follows the timetable of the highest variation type included in the grouping. [12]

The specific case of groupings of purely national marketing authorisations is described in article 13d of the *Variation Regulation*. [7]

2.2 Application for Worksharing

Worksharing procedures are either coordinated by the EMA, if a centrally authorised product is included, or by the CMDh, if only nationally authorised products are included.

The submission of a worksharing is made to the NCAs of all Member States concerned in the procedure. For worksharing, the *Reference Member State* is usually called the reference authority, but both terms are sometimes used synonymously. The reference authority takes the lead in the assessment and takes care of the validation of the application. In the validation phase, it

examines the application in line with the validation procedure followed for Type II variations (chapter 2 of the *Best Practice Guides* of the CMDh) and checks for any missing documents. If documents are incomplete, the applicant can usually file them later during validation, but this may delay the start of the procedure. As distinguished from the assessment phase (procedure), during validation, no content-related scientific analysis is performed. [8] [13]

Once the procedure has started, independent from the variation type applied for, it follows the timeframe of a Type II variation, i.e. an initial assessment phase of 60 days, a possible clock-stop and another 30 days as 2nd assessment phase, which is then followed by either an approval, a refusal or a referral (see also sections 4.4.1 and 4.5.1). [1]

Worksharing procedures of 30 days (urgent safety related procedures) and 90 days (e.g. change or addition of an indication) are also generally possible.

During a 60-day procedure relevant authorities are requested to approve or send additional comments to the FVAR (Final Variation Assessment Report) of the reference authority within 20 days (Day 80). In case PSRPH (Potential Serious Risk(s) to Public Health) are identified, the CMS may ask the reference authority to refer the application to the CMDh, resulting in a referral (see also section 4.5.1). In the case of at least one centrally authorised product the opinion of the CHMP has to be recognised by the CMSs.

Worksharing is possible for products approved through the Centralised Procedure (CP), Mutual Recognition Procedures (MRP), Decentralised Procedures (DCP) or authorised purely nationally and can also be combined among these authorisation types. It is an optional procedure, but there are instances when it is highly recommended.

Variations of Type IB and Type II and groupings can be included. Type IA variations (unless part of a grouping) and line extensions (extension applications) are excluded from worksharing.

All grouped applications are allowed for worksharing because groupings essentially define what is placed in an application and worksharing defines how the application is evaluated and by whom. The condition is that the same change(s) must apply to all products included in the procedure.

If the same change to different MAs would require submission of individual supportive data sets for each product and separate product-specific assessment, such changes would not benefit from worksharing. [1]

The most important guidance for the submission and handling of worksharing procedures for NAPs is chapter 7 of the *Best Practice Guides* of the CMDh. For CAPs, it is the Q&A section of the EMA on worksharing. [8] [3]

For NAPs, the submissions are made through the *Central European Submission Portal* (CESP) and for CAPs, submission is made through the *eSubmission Gateway* directly to the EMA. [14] [15]

2.3 Statistics – WS Procedures by Time Period and Type

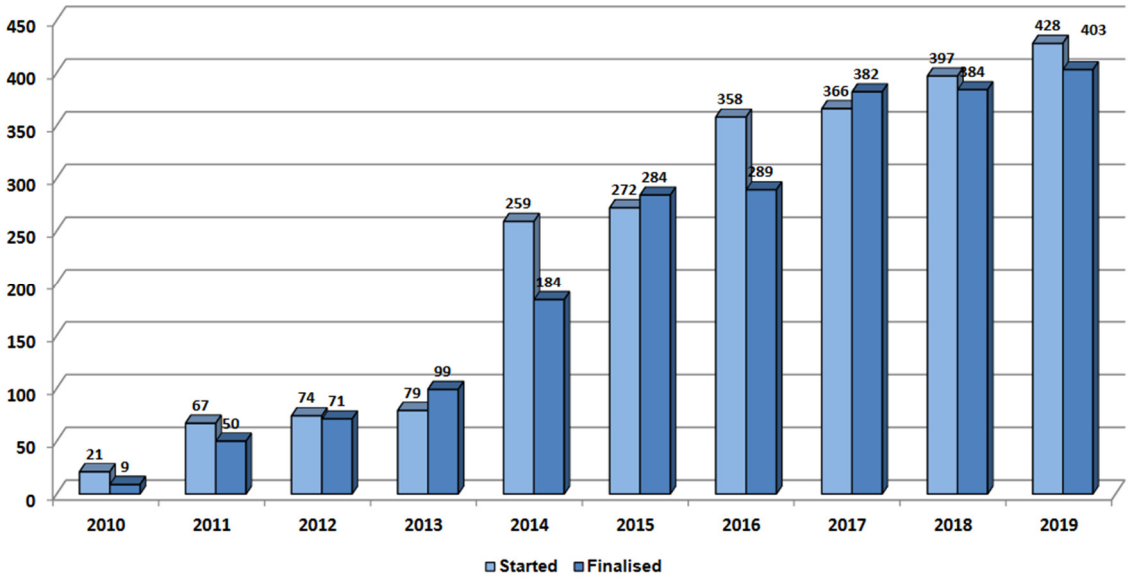

Figure 2 Number of WS Procedures by Year

[16]

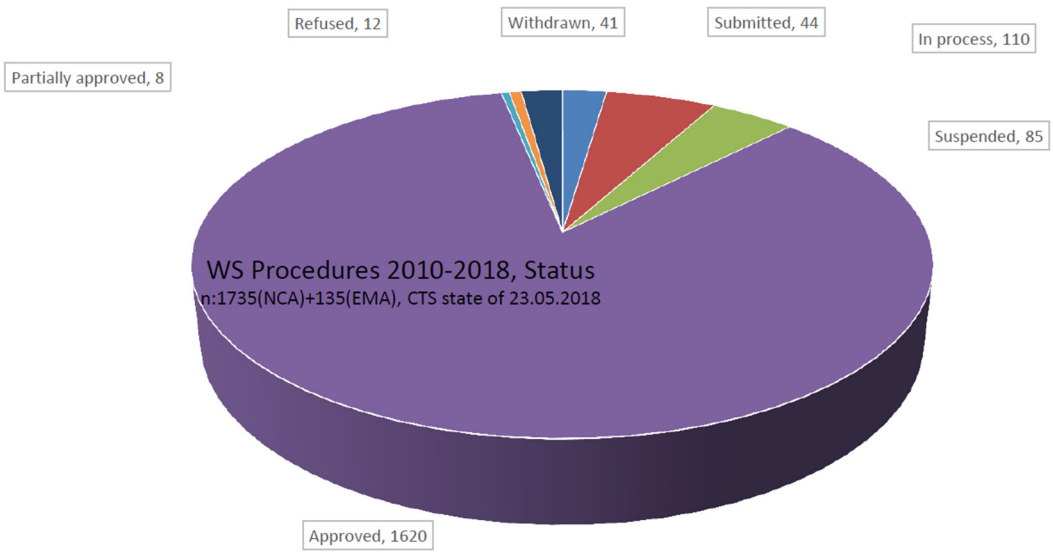

Figure 3 Status of WS Procedures 2010-2018

[17]

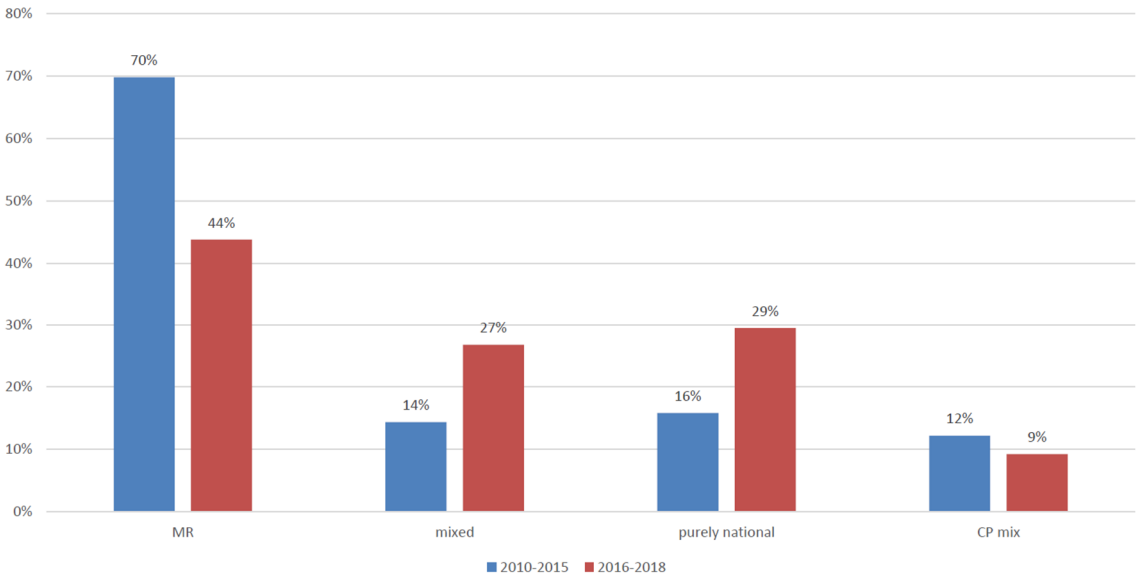

Figure 4 WS - product composition - relative comparison by period

[17]

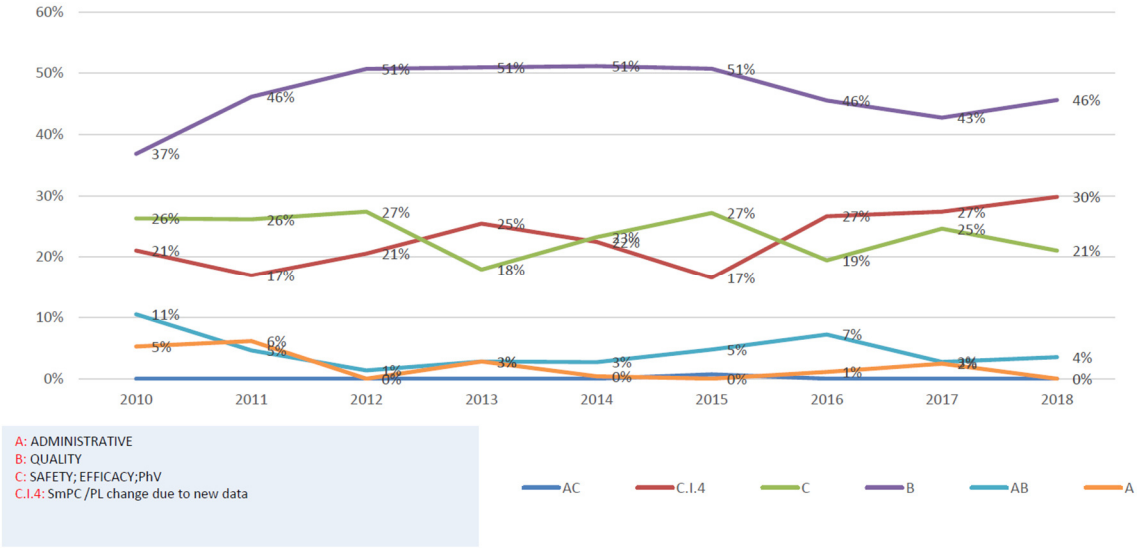

Figure 5 WS - relative distribution of scope

[17]

The graphs shown above (Figures 2 – 5) feature started and finalised WS procedures by year, the status of WS procedures started between 2010-2018, a relative comparison of product composition (by authorisation type) between 2010-2018 and the relative distribution of the scope, i.e. the nature of the requested change to the product.

It is apparent that the number of started and finalised worksharing procedures has risen since their implementation in 2010. However, during the last 3 years, no major increase could be recorded.

Looking at figure 3, the majority of procedures was completely approved (1620 = 86.6 %) and only a very small number was refused or partly approved (12 refused = 0.6 %; 8 partially approved = 0.4 %). It is also worth noting that 110 procedures were still in process at the time of May 2018.

From the product composition in worksharing a trend towards less MR-products and more mixed and purely national products is visible. The most drastic change can be observed with MR-products, as their inclusion in WS have dropped by 26 percentage points. Overall, less CP products seem to be included in mixed applications with nationally authorised products now than it was the case between 2010-2015.

Figure 5 shows the relative distribution of the scope. Since 2010 the magnitude of the different scopes has remained the same to some degree. Although quality changes are still the most relevant types of changes for worksharing, a decline of a few percentage points can be observed for the previous years.

3 The Quality Dossier

3.1 Common Technical Document

The Common Technical Document (CTD) is a general technical format which combines all the information on quality, safety and efficacy of a medicinal product. It has revolutionised many processes such as harmonised submissions and review processes. This factor has made good review practices possible.

Since July 2003, the CTD has become the mandatory format for new drug applications in the EU and Japan. Since January 2019, the electronic version (eCTD) has become mandatory as well. It is used for almost all regulatory submissions. Each submission is divided into sequences, starting with *0000*.

[18] [19]

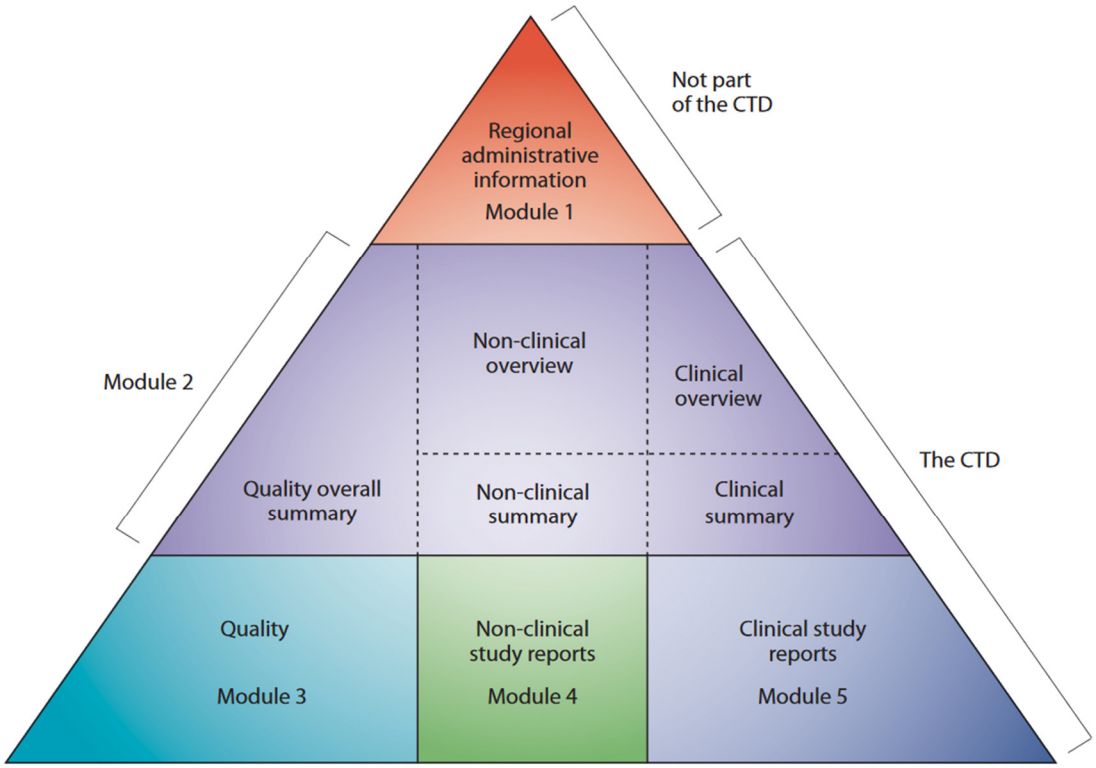

Figure 6 Common Technical Document

[18]

The CTD consists of 5 Modules. Modules 2-5 are common for all regions where the format is being used whereas Module 1 is region specific. For example, Module 1 is identical throughout the European Union.

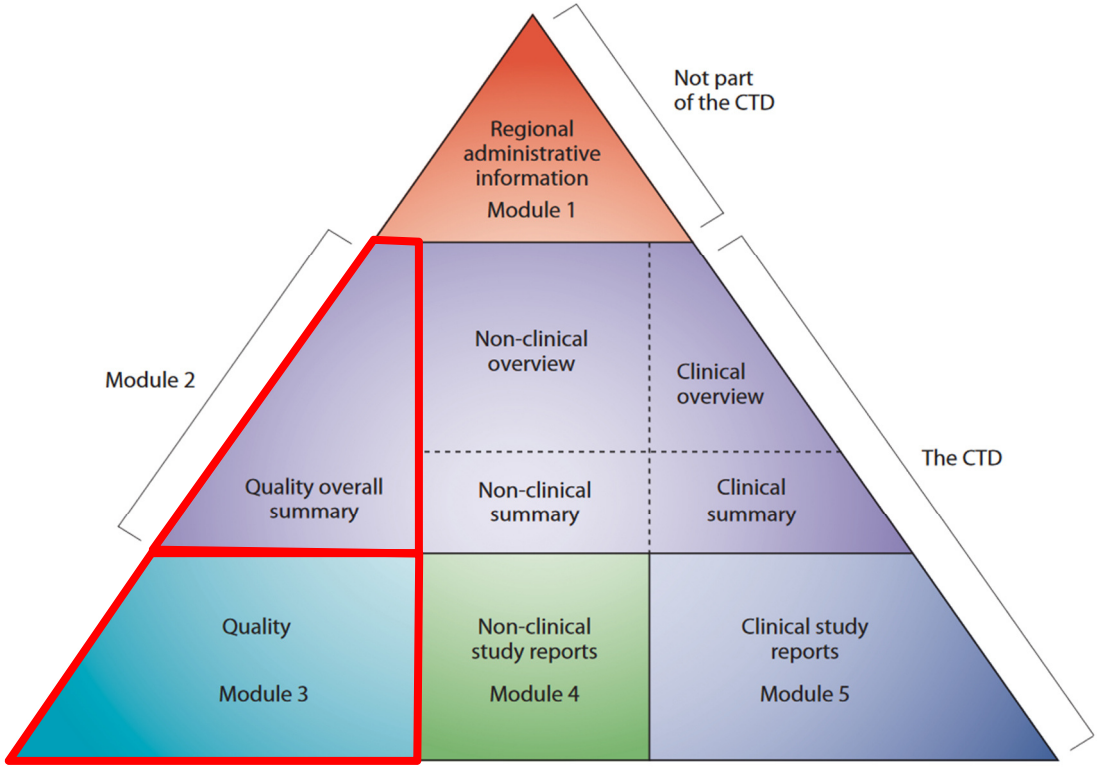

Figure 7 Quality Part of the Dossier

The quality part of the dossier is also called Module 3 or CMC. It includes information on the active substance(s), the excipients, the manufacturing process, validation of procedures, controls etc.

There is also Module 2.3, which contains the Quality Overall Summary.

3.1.1 Quality Overall Summary (Module 2.3)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should provide an overview to the quality reviewer, including justifications where guidelines were not followed, discussions of key issues and

cross-references to volume and page number of the relevant module, including other modules than Module 3 (if applicable).

The QOS should usually not exceed 40 pages of text, unless it concerns a biotech product, where the page number should not exceed 80.

It is structured into an introduction, a drug substance section, a drug product section, appendices and a general information part.

The introduction should include the proprietary name, non-proprietary name or common name of the drug substance, the company name, the dosage form(s), strength(s), route of administration, and proposed indication(s).

The drug substance section contains descriptions and information on the active ingredient, e.g. manufacture, characterisation, stability etc.

Descriptions and information on the finished product and the excipients, e.g. composition of the drug product, manufacture, stability etc., are included in the drug product section.

A summary of facility information (relevant only to biotech drugs) and a part on adventitious agents' safety evaluation (if applicable) should be provided in the appendices and a brief description of the information relevant for the specific region should be provided in the regional information part. [20]

Module 2 not only consists of the quality section, but also includes overviews and summaries on Module 4 (preclinical) and Module 5 (clinical).

3.1.2 Chemistry, Manufacturing and Controls (Module 3)

Module 3 is structured very similarly to Module 2.3. It consists of a Table of Contents (3.1) and the Body of Data (3.2). The Body of Data is divided into Drug Substance (3.2.S), Drug Product (3.2.P), Appendices (3.2.A), a part on Regional Information (3.2.R) and Literature References (3.3).

As with the QOS, not all sections are relevant to all types of drugs.

Module 3 contains the raw data on quality and manufacturing aspects as well as descriptions and justifications. For combination products there is one drug substance section per active ingredient and each manufacturer requires their own manufacturer section. The full structure of Module 3 is as follows:

3.1. TABLE OF CONTENTS OF 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 Characterization
    - 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
- 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.2.1 Components of the Drug Product
    - 3.2.P.2.2 Drug Product
    - 3.2.P.2.3 Manufacturing Process Development
    - 3.2.P.2.4 Container Closure System
    - 3.2.P.2.5 Microbiological Attributes
    - 3.2.P.2.6 Compatibility

- 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.4.5 Excipients of Human or Animal Origin
  - 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 Characterization 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 Conclusion
  - 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.1 Facilities and Equipment
- 3.2.A.2 Adventitious Agents Safety Evaluation
- 3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.3 LITERATURE REFERENCES

[20]

4 Module 3 Harmonisation

4.1 Regulatory & Legal Background

This section and the following sections will focus on NAPs, especially on purely nationally authorised products. General points of consideration for CAPs and worksharing are mentioned in section 2.

Before any variation or worksharing can be submitted it needs to be categorised properly. In order to achieve this, the *Classification Guideline* should be consulted (see also section 2.1.2).

However, there is no exact way to classify a Module 3 harmonisation by means of the worksharing procedure with the help of the *Classification Guideline*. The closest category is B.V.b.1: *Update of the quality dossier intended to implement the outcome of a Union referral procedure* (Figure 8). However, in this case we are dealing with the voluntary form of Module 3 harmonisation and not with the mandatory type after a referral.

B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The change implements the outcome of the referral	1	1, 2	IAIN
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it			II

Figure 8 Classification Guideline 1

[10]

When there is no exact category that is applicable one needs to consider other sources of information, i.e. article 5 recommendations from the CMDh or Q&A-documents from the EMA or the CMDh. Article 5 recommendations are propositions of the CMDh for the classification of variations that are unforeseen, i.e. not or not yet included in the *Classification Guideline*. They are regularly updated and can be found on the CMDh's website. [21]

In this particular case, the *Q&A-List for the submission of variations according to Commission Regulation (EC) 1234/2008* of the CMDh provides the answer:

Question 4.16

Under which category can I submit a variation or worksharing application for a harmonisation of the quality dossier when the products concerned were not part of an Article 30 (human) or Article 34 (veterinary) referral?

If the concerned nationally authorised product or products owned by the same MAH have not been part of a referral, they may also be submitted as a single Type II variation in a worksharing procedure. The category shall be B.V.b.1.z. The updated dossier may be included in the worksharing to adapt all products in the worksharing to that version, leading to no changes on the already updated products.

Other adaptions to Module 3 not including harmonisations are not applicable to this procedure and should instead be submitted as groupings indicating every single change in the dossier as single variations. The *Classification Guideline* shall be used to classify these variations.

As it is a z-category, the conditions and documentation requirements stated in the guideline are not applicable (see Figure 9).

Conditions

1. The outcome does not require further assessment.

Documentation

1. Attached to the cover letter of the variation application: a reference to the Commission Decision concerned.

2. The changes introduced during the referral procedure should be clearly highlighted in the submission.

Figure 9 Classification Guideline 2

[10]

Question 4.5

Can harmonisation of Module 3 be done by worksharing?

Answer: *Module 3 harmonisation* ***is surely an option for worksharing*** *as worksharing does not require product harmonisation in advance. The aim is to have a harmonised result.* [4]

To sum up, the worksharing procedure is a viable way of performing a Module 3 harmonisation of different (national) marketing authorisations owned by the same holder.

4.2 Why Harmonise the Quality Dossier?

There may be several reasons for conducting a Module 3 harmonisation, the most obvious being to have a harmonised result/outcome. The quality part of different (nationally authorised) products would be aligned and maintenance and future variations to change the quality information would be facilitated.

But the less obvious manufacturing point of view may have an even bigger impact. If the products are all manufactured at the same site, it is essential that the dossiers are mostly aligned because it is unfeasible to produce different batches according to separate dossiers.

The unlikely circumstance that the same product is manufactured at different sites in different Member States may lead to an unfeasibility of the consolidation endeavour. More information is provided in section 4.3.

Prior to conducting a Module 3 harmonisation, one needs to assess if the alignment of the quality dossiers of different (national) marketing authorisations should be prioritised. The following decision tree can provide initial guidance.

4.2.1 Decision Tree

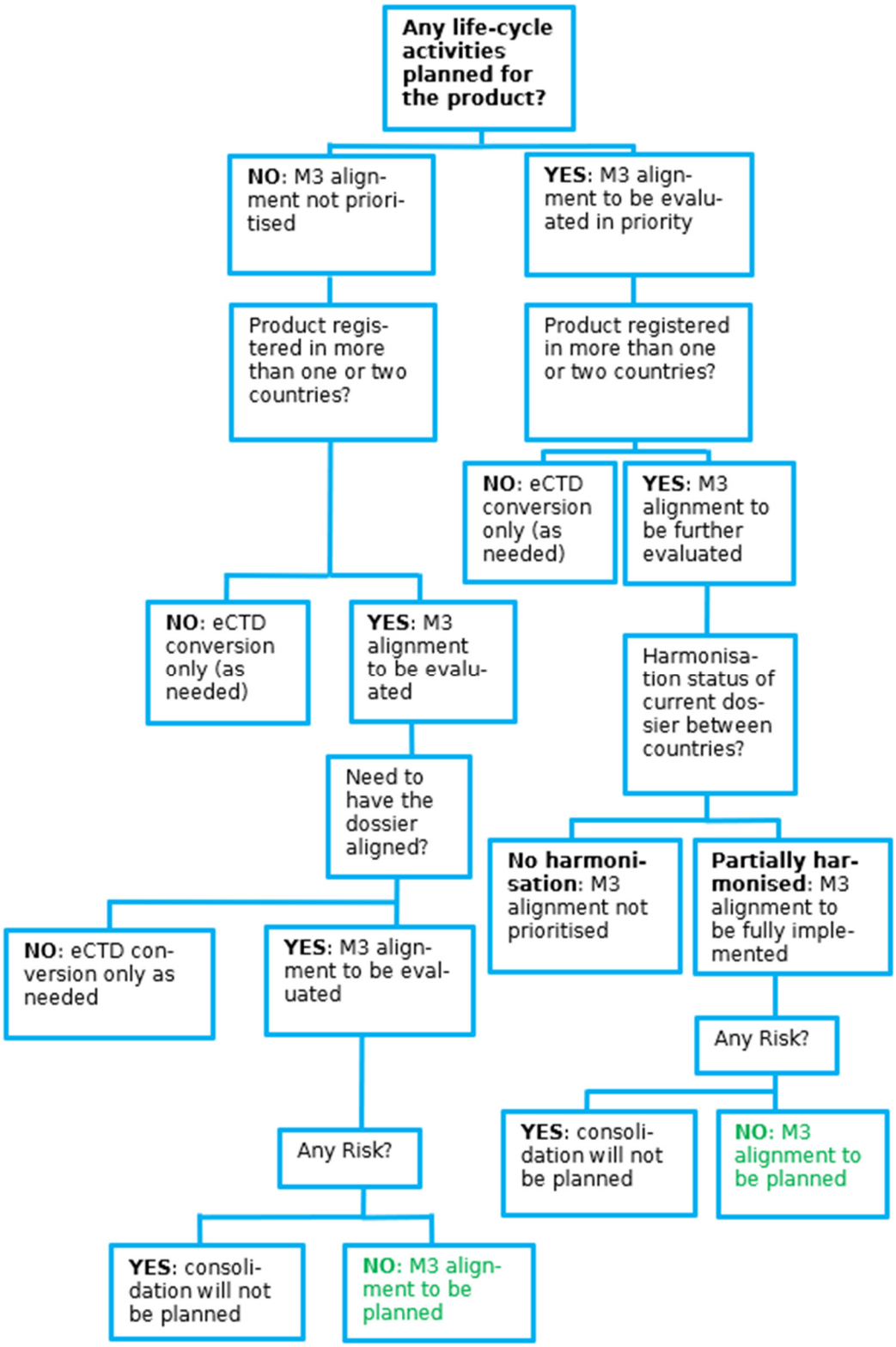

Figure 10 Harmonisation Decision Tree

[Adapted from [22, p. 26]]

No harmonisation and *partial harmonisation* are referencing the current alignment status of the quality dossier between the affected countries. If no sections are harmonised at all, e.g. if there is one manufacturing site for each product in each country or there is completely different stability information, going through with a worksharing procedure may not be sensible.

But, if only one or two sites manufacture the product for all Member States where it is marketed, the products would greatly benefit from a consolidation of the quality dossier.

If no or negligible risks are identified, the Module 3 alignment can be planned. Further information on risks and the gap analysis in general can be found in the next section.

4.3 Pre-Submission Activities

4.3.1 Gap Analysis and Possible Show-Stoppers

Before submitting a worksharing a gap analysis of the different dossiers should be performed and possible show-stoppers identified. It is a very important step to be well prepared for the desired procedure.

The analysis is done by contrasting the contents of Module 3 of products authorised in different Member States. The comparison is important because the applicant needs to know the state of the sections in question to be able to identify the changes needed. It can also help to identify show-stoppers that could jeopardise the harmonisation procedure.

Differences in the dossier may originate from different competent authorities and different dates of marketing authorisations and thus divergent states of science and technology at the time of approval. These circumstances occur predominantly in purely nationally authorised products and less in products authorised via MRP, DCP and CP, as there is only one authority involved.

The gap analysis is usually performed by CMC managers (if available) because of their expertise in the quality field.

The reference dossier will need to be aligned to all the current guidelines including ICH. If not, the rebound effect could be very strong, especially in case of numerous countries involved in the procedure. In any case, the decision of

the reference authority will heavily influence all licenses included in the harmonisation.

Another noteworthy aspect is that a change affecting only a single product in a country might be implemented to all other authorisations. If the change pertains to the most recent guidelines or a state-of-the-art procedure, it is usually advantageous. But if this is not the case, there is a chance that an outdated section or procedure of a product registered in one or more countries may be implemented in all other products. This risk is amplified through the fact that no Member State can be withdrawn from the procedure once the worksharing has started. In case the MAH wishes to withdraw, they will need to withdraw in all MS (including the RMS). [8]

The applicant should also check for the validity of all certificates including GMP certification and make sure that they do not expire during the procedure or this could also turn out to be a risk.

An example of a gap analysis for a product registered nationally in 4 EU-countries could be the following:

Product X, Strength Y				
	Approval Status			
Mod3 section	**Italy** Marketed: Y/N	**France** Marketed: Y/N	**Germany** Marketed: Y/N	**Spain** Marketed: Y/N
32P31	Mfg site A Mfg site B - QC Testing A	Mfg site A Mfg site B Batch release A QC Testing A	Mfg site A Mfg site B Batch release A QC Testing A	Mfg site A - Batch release A QC Testing A
32P32, mfg site A	Batch size A Batch size B -	Batch size A - Batch size C	Batch size A Batch size B -	Batch size A Batch size B -
32P32, mfg site B	Batch size A Batch size B	Batch size A Batch size B	Batch size A Batch size B	- -
32P51	SpecsA	SpecsA	SpecsB	SpecsC

32P8	Shelf life 36M < 30 °C	Shelf life 36M < 30 °C	Shelf life 36M < 30 °C	Shelf life 24M < 30 °C
32R	CEP API mfg site A CEP API mfg site B	CEP API mfg site A -	CEP API mfg site A CEP API mfg site B	CEP API mfg site A CEP API mfg site B
32XX	XX	XX	XX	XX

Table 1 Gap Analysis

After the gap analysis all changes needed for alignment to the target dossier including the impacted country should be categorised and listed, e.g. introduction/deletion of a manufacturing site or batch release site, tightening of specification limits, addition/update of CEPs etc.

The list of changes can be included as annex to the application form when the submission to the respective authority is performed. That way not all changes have to be listed in detail in the application form (see section 4.4.1).

A general suggestion can be given that the dossier that is most up-to-date should be used as a reference and that all others ought to be adapted to it. Then, also the reference authority from that specific Member State could be used, which could greatly facilitate the procedure. If there is not one dossier that is state-of-the-art, the MAH can either decide to update one dossier to the most current scientific status by submitting the appropriate variations beforehand and aligning all other dossiers to it within the harmonisation procedure, or the alignment could be performed section by section. For example, when looking at table 1, by aligning section 32P31 of all products to that section of the German product, section 32P51 to the French and Italian products etc.

If this approach is not feasible at all, the submission of the Module 3 harmonisation may need to be postponed.

4.3.2 Most Common Deficiencies in Module 3

The previous section dealt with the general approach to the harmonisation process of the quality dossier, possible show-stoppers and risks on behalf of the applicant. In this section the perspective of the authorities will be addressed. This point of view should also be taken into account, especially when preparing the target dossier for the consolidation.

According to an experienced quality assessor of the BfArM, the most common deficiencies in the quality dossier one needs to be aware of include, but are not limited to, the following:

Drug substance:

- Starting materials
  - Only a one-step synthesis described (generally not acceptable without a CEP)
  - Insufficient specifications
  - Missing details on manufacturer/supplier
  - Lack of details and/or poor description of the manufacturing process of the substance from the introduction of starting materials
  - Starting materials not acceptable (i.e. not selected according to ICH Q11) [23]
- Impurities
  - Missing details on single impurities
  - Limits and/or testing for drug substance not in line with Ph. Eur. monograph
  - Missing discussion on mutagenic impurities
  - Insufficient discussion on carryover effect of impurities coming from the starting material
- Control of drug substance
  - Insufficient demonstration that residual solvents are removed
  - Lack in description of analytical method
- Reference standards or materials
  - Missing characterisation
  - Missing information on plausibility of a given assay for an in-house reference standard
- Stability
  - Container closure system not suitable for the drug substance

  - Reference to different specification limits for release and during stability studies
  - No tests under accelerated conditions performed

Drug product:

- Pharmaceutical Development
  - Discriminatory power of a method used for the dissolution testing not documented (method should distinguish “good” and “bad” batches)
- Specification
  - Dissolution test (limits set are too wide, not set according to results from clinical batches)
  - Impurities (limits set for degradation products are too wide)
- Elemental impurities
  - Missing risk evaluation (Guideline ICH Q3D) [23]
  - Control strategy not sufficiently described
  - Missing data of production/pilot batches
- Validation
  - Missing data on validation of Karl-Fischer-Titration for determination of water content in tablets
  - Missing data on validation of method used for determination of microbial count
  - Deficiencies concerning validation data for determination of impurities (specificity, range, linearity, accuracy, precision, quantification limit)
- Reference standards
  - Source, purpose or characterisation is not sufficiently described
  - Reference standard of Ph. Eur. monograph is used without demonstration of suitability for the drug product
- Stability
  - Limits for degradation products not set in accordance to batch data
  - Missing qualification for degradation products
  - No justification for widening of range for assay

[24]

4.3.3 Cost Analysis of EU-Countries

Procedural fees may not be the biggest issue whether or not to decide to proceed with a worksharing or not, but it may still be worth to analyse them prior to submission. The analysis shows that there are great differences between different MS. It is worth noting, however, that the fees are limited by the fact that a M3 harmonisation is classified as a single Type II variation.

Some authorities (like the BfArM) do not demand payment of the fees before the submission, instead a payment should be made upon receipt of the relevant invoice. For most others a proof of payment should be added to the application form or the cover letter (see also section 4.4.1).

Country	Costs Type II Worksharing [B.V.b.1.z]	Comments
AT	Included in annual fees	
BE	BE=RMS: **6070.41 €** or **10221.90 €** BE=CMS: **532.35 €** or **1354.59 €**	Clinical Type II more expensive than analytical Type II
BG	ca. **700 €**	
CY	National products: **51 €** MRP/DCP: **341 €**	
CZ	ca. **2142 €**	
DE	DE=RMS: **7500 €** DE=CMS: **2800 €**	
EE	**16 €**	
EL	**2000 €** for NP/MRP/DCP	It may depend on the procedure, especially for NP
ES	**7265.40 €**	
FR	**3500 €**	Price per product
HU	ca. **1005 €**	
IT	MRP IT=RMS: **24639.22 €** NP/MRP IT=CMS: **20532.70 €**	
LT	**1400 €**	
LU	**150 €** / Type II variation	Half yearly payment
LV	Included in annual fees	
NL	Included in annual fees	

NO	NO=RMS: **12681 NOK** NO=CMS: **10568 NOK**	Equal to approximately 1141 € / 951 €
PT	ca. **1585.65 €**	
RO	ca. **1600 €**	
SE	SE=RMS: **55000 SEK** SE=CMS: **8000 SEK**	Equal to approximately 5500 € / 800 €
SI	**700 €**	
SK	**3200 €**	

Table 2 Cost Analysis

No data available for DK, FI, HR, IE, IS, PL.

[adapted from an in-house survey for the European affiliates of a global pharmaceutical company [25]]

4.3.4 Letter of Intent

The letter of intent lets the preferred reference authority know that the company wishes to apply for a worksharing procedure. Previously, the letter had to be sent to the CMDh at least 2 weeks prior to the next meeting. If no centrally authorised product was to be included in the procedure, the applicant was able to give a recommendation on NCA, but the CMDh would ultimately decide. Usually, the preferred reference authority would have been chosen.

As of June 2019, the Letter of Intent does no longer have to be sent to the CMDh, but rather can be sent directly to the preferred reference authority. [8]

It should still be sent at least two weeks before applying for the procedure. For bigger procedures, prior notification and advice through a telephone conference or an on-site meeting with the desired reference authority may be carried out.

A template for the Letter of Intent is available on the CMDh's website. [26]

The applicant needs to specify its name and address as well as the contact details of the dedicated contact person. Then, the type of variation following the worksharing procedure (Type II, Type IB or grouping) needs to be named, as well as a list of every single variation included in the worksharing procedure, including the details from the *Classification Guideline*.

The concerned products need to be stated, as well as their active substance(s), their MRP/DCP number (if they are authorised via MRP/DCP) or the

national MA number including the Member State (if they are authorised purely nationally).

Then, justifications for the WS and the grouping (if applicable) need to be given. They should include a detailed scope and background for the proposed changes as well as the intended submission date of the WS.

Finally, the applicant needs to name the preferred reference authority and give an explanation that all marketing authorisations belong to the same MAH.

Either the letter of intent or the e-mail by which it is sent should include the request for the worksharing procedure number. An example of a procedure number with DE=RMS is *DE/H/XXX/WS/123*. The number at the end may give an idea on the total number of WS performed by that specific reference authority.

The desired reference authority will answer to the request and state the procedure number within 7 days via the CMDh's secretariat. The CMDh will then formally confirm the procedure during its next meeting.

The responsibility of agreement for a procedure lies with the CMDh. Even if the desired reference authority has already agreed to the conduction of the WS, the CMDh may still decline the allocated reference authority in its meeting. This case should however be considered unlikely. [8]

4.3.5 Advice Procedures

Because 2 weeks' time for a reference authority to decide whether to accept the RMS-ship or to decline it is rather short, a consultation between the applicant and the preferred reference authority may be advisable. The need for a discussion is of course linked to the complexity of the procedure and the magnitude of the changes.

Advice procedures are usually available at every NCA as well as at the EMA. The BfArM, for example, offers both scientific advices and pre-submission meetings. [27]

In case of questions prior to the procedure, the contact information published on the CMDh's website can be used. An alternative could be to check mailing lists directly on the website of the respective NCA. During the procedure, contact details are stated in the assessment reports (see also section 4.5.2). [28]

The CMDh may – on its own initiative or if requested by the MAH – also give advice directly on the suitability and/or practicability of the proposed work-sharing procedure. [8]

4.3.6 Other Pre-Submission Activities

Other activities to be performed by the applicant include the creation or update of the target eCTD-dossier. This could also mean correction of typographical errors and/or reformatting of the dossier.

Future steps during and after the procedure should also be planned in advance, like the implementation of the changes on-site, i.e. on the manufacturing level.

Another important aspect is the countries that are to be included in the work-sharing. Not all countries that may be affected due to the fact that a similar product is authorised there have to be included in the procedure. The expected national approval in a specific country can also play a role. These aspects should be well thought through, as single MSs cannot be withdrawn during the procedure (see also section 4.3.1). [8]

4.4 Application for Module 3 Harmonisation

The Information in this section is based on actual worksharing performed by a global pharmaceutical company. [29]

4.4.1 Application & Documents to be Submitted

As previously stated in section 2.2, the application for NAPs is submitted through the Central European Submission Portal (CESP) to all Member States concerned. If applicable, local submissions also need to be made. Some MSs even require the submission of originally signed documents. This case needs to be checked in advance in order to not jeopardise the validation process.

Most regulatory submissions are performed electronically through CESP. Before submission, the applicant needs to first create a so-called *delivery file*. It includes information on the kind of authorisation, the type of

change/submission, the national competent authorities the submission should be made to and a submission specific CESP number. The site also includes an FAQ section as well as training on demand videos. [14]

The documents to be submitted are generally the same as for other variation procedure types (BPGs chapters 3, 4 and 5), i.e. the common cover letter (CL), the common application form (eAF), separate supportive documentation sets and revised product information (if applicable) and mock-ups or specimens (if applicable). If only purely national marketing authorisations are involved, the proposed changes to the product information should be described in detail in English in the *Present-Proposed* box of the application form. [8] [13]

In addition to the documents mentioned above, for Module 3 harmonisations, one should also submit the relevant page of the *Classification Guideline*, the Q&A section (i.e. question 4.16) and a list of all the changes to the DS/DP as well as justifications for them and CEPs or other certificates (if applicable). If the list of changes is added as annex to the application form, notice should be made in the *Present-Proposed* box, thus avoiding the need to list all changes there. Most countries require the payment of procedural fees prior to submission and a proof of payment (PoP) should therefore be added as annex to the application form. If the fees are payable annually or the respective NCA sends out an invoice to the MAH, no PoP is required.

The cover letter should include the type of variation, the procedure number, the RMS (reference authority) and the CMSs, all affected products and their respective Member States and NCAs. It should also consist of the eCTD sequence numbers, the CESP numbers and a list of all documents that are submitted including annexes.

According to guidance, only one contact person needs to be stated in the application form for WS procedures. In other applications, usually one contact person is named per Member State. [30]

General guidance on filling out application forms can be found on the CMDh’s website. [30]

4.5 Procedure

The *procedure* refers to the time period when the assessment begins (Day 0) until the opinion of the reference authority and closure of the European part of the procedure. After the European approval by the reference authority, a national phase may follow – e.g. if changes to the product information are involved. Before the procedure begins there is the validation phase, where the application is checked for completeness. If documents are missing or are incomplete, procedure start is delayed.

4.5.1 Timetable

Worksharing procedures generally follow the timetable of a Type II variation even if the highest single variation within the worksharing is only a Type IB. However, in case of a Module 3 harmonisation, the variation is classified as a single Type II anyway (see section 4.1).

The assessment period until an opinion is reached takes a minimum of 60 days (30 days, in the unlikely event of a shortened timetable). A clock-stop is possible if questions are raised by the NCAs (see also section 2.1.2) [8]

Concerned Member States have 20 days to comment the FVAR of the reference authority. They may also raise Potential Serious Risks to Public Health (PSRPH), but not later than Day 90. In this case the reference authority will request a referral to the CMDh.

Day in Procedure	Description
Day 0	Start of the Procedure. The timetable is notified to the CMSs and to the MAH by the RMS
Day 40	The Preliminary Variation Assessment Report (PVAR) is circulated to the CMSs and to the MAH
Day 55	CMSs send comments (if applicable) to the RMS
Day 59	Request for Supplementary Information (List of Questions) is sent to the MAH and to the CMSs, clock stop begins
Clock off period	Not more than 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the Final Variation Assessment Report, FVAR)
Day 60	Restart of the Procedure, the RMS circulates the FVAR to the CMSs and to the MAH

Day 75	Possible break-out meeting to discuss still open points of discussion
Day 80	CMSs send comments (if applicable) on the FVAR to the RMS
No later than D90	CMSs may disagree on the opinion of the RMS on the grounds of PSRPH. Then the application is referred to the CMDh by the RMS
Day 90	The reference authority circulates the final opinion to the CMSs and to the MAH. If applicable, the MAH shall provide the updated SmPC and/or labelling to the RMS and CMSs If not referred to the CMDh, the final opinion is considered approved by the CMSs.

Table 3 Timetable (60 days)

[adapted from [8]]

4.5.2 Preliminary Variation Assessment Report

The Preliminary Variation Assessment Report (PVAR) is sent on Day 40/15/70 of the procedure (depending on the procedure type) from the reference authority to the Concerned Member States as well as to the applicant. It includes the administrative information on the procedure (name of the product and active substance(s), procedure manager and assessors including contact information, MS concerned and the nature of the requested change(s)). Then, there is the recommendation, i.e. if the procedure is considered approvable or not at this point in time of the procedure. If it is not approvable (because major objections are present), that does not mean that the procedure won't be approvable at a later point in time.

The PVAR also includes an executive summary of the procedure with a detailed scope of the variation. Another section is the scientific discussion, which only includes quality aspects in the case of a Module 3 harmonisation (unless product information is also involved). The scientific discussion states the documents provided by the applicant and the reference authority's comments on them. After the discussion, an overall conclusion and a benefit-risk assessment is given. According to *Directive 2001/83/EC* (as amended), the benefit-risk assessment must always be in favour of the benefit for approving the procedure. [9] [31]

Finally, the request for supplementary information (RSI, proposed by the reference authority) is released.

4.5.3 CMS Comments and Clock Stop

After the PVAR is released by the reference authority the CMSs have time until Day 55 of the procedure to comment on the PVAR and request further information of their own. The applicant is then asked to address these comments as well in the Day 59 clock stop e-mail. In many cases the CMSs endorse the opinion of the reference authority and do not raise comments of their own, however.

During the clock stop period the applicant has 60 days to answer the questions and send amended documents. This period may be extended if the applicant proposes it and it is granted by the reference authority. After that, the authority has another 60 days to create and circulate the FVAR.

The requests for supplementary information (list of questions) are highly individual and based on the scope and extent of the proposed changes. The applicant is well advised to plan its resources for this period well ahead of time.

All relevant documents needed for the responses should be sent within an eCTD sequence through CESP. For a better overview for the assessors it is also advisable to attach a document answering all questions and referring to the annexes in which the supporting documentation can be found. [19]

If no questions have been raised by the RMS or the CMSs it is also possible that the procedure ends on Day 60.

4.5.4 Final Variation Assessment Report

The FVAR is released on Day 60 of the procedure. With its circulation to the CMSs and the MAH the procedure is restarted. Again, CMSs have the opportunity to comment on the RMS' opinion (until Day 80). On Day 75 a possible break-out session may be held to discuss still open points, as applicable.

The FVAR is structured exactly like the PVAR, except that the *Scientific Discussion* is replaced by *Assessment of the Responses to the Member State(s) Request for Supplementary Information*. In this section, the major objections, minor objections and other concerns previously raised are stated as well as the respective responses by the applicant. The responses are then commented by the relevant assessor and evaluated, if they have adequately addressed the open issues or if further explanation is required.

If some objections have not been addressed properly, the applicant may be given another time period without any further prolongation of the timetable in case of NAPs to respond once more, with the addition of another round of CMS comments. If this is the case, the FVAR is updated again before finalisation.

4.5.5 End of Procedure

The procedure either ends with the approval of the reference authority, a refusal or a referral. Usually, an EoP e-mail is sent out stating the approval date and informing the CMSs and the applicant. Then, the assessment on European level is concluded and the national approvals follow next.

4.6 Post-Authorisation

The post-authorisation period refers to the phase after the RMS-approval. This is the phase where post-approval measures are taken, such as the implementation of the changes on manufacturing level. Before this can be undertaken, however, generally every single Member State that took part in the procedure has to first approve on national level. If there is no impact on the product information the RMS-approval is often considered the national approval as well. However, this is not the case in all countries (see Table 4 below).

If there is an impact on the product information there is usually a national phase where the translations are submitted to the respective authority. In that case the national approval is considered the date when the translations are approved in that country or at the latest after 30 days after submission according to the BPG chapter 7. [8]

The time period of 30 days is not only stated in the BPG, but also embodied in the law and is thus legally binding. Article 23 of the *Variation Regulation* addresses the implementation of the changes on NCA's side (*Amendments to the decision granting the marketing authorisation*) and article 24 addresses the implementation period of variations for the applicant, more specifically article 24.3b subject to worksharing. [2]

In case of doubts, a risk evaluation should be performed before the planning and submission of the procedure weighing up the possible risks to implement

the changes (approved by the reference authority) nationally without an official national approval.

4.6.1 National Approvals of EU-Countries

Country	National Approval Type II Worksharing [B.V.b.1.z]	Comments
AT	RMS approval date = national approval date	For text changes it depends on the type of variation
BE	RMS approval date = national approval date	For a Type II, texts need to be sent to the National Authority after RMS approval. Approval of the texts will be granted between ca. 1-3 months
BG	Grouping Type IB approval: 3-12 months Grouping Type II/IB approval: 3-12 months	
CY	3-6 months depending on the HA workload	
CZ	Grouping Type IB: Within 30 days of sending the positive / partially positive final opinion of the reference authority Grouping Type II/IB: Within 30 days of sending the positive / partially positive final opinion of the reference authority	Applicable, when change not related to texts
DE	RMS approval date = national approval date	In case of impact on product information: short national phase that usually does not exceed 30 days
EE	Grouping Type IB will be nationally implemented by SAM within 30 days. MAH can implement 30 days after RMS approval even if not yet implemented by local HA Grouping Type II/IB will be nationally implemented by SAM within 60 days, MAH can implement after local approval	SAM = Estonian State Agency of Medicines
EL	Usually more than 1 ½ years	Depends on impact on product information or not. Difficult to predict.
ES	3 months on average	

FR	For grouping of Type IB impact on PI: 30 days after submission of national translations no impact on PI: implementation immediatly after RMS positive opinion For grouping of Type IB/II impact on PI: 30 days after submission of national translations no impact on PI: implementation 30 days after RMS positive opinion	In practice, due to previous experiences, some delay may be expected
HU	Grouping Type IB – officially, the timeline according to the EU regulations are followed Grouping Type II/IB – officially, the timeline according to the EU regulations are followed	In practice, some delay may be expected but not significant
IT	Around 6 months in the case of PI impact or change to the MA; if there is no PI impact or change to the MA, the change could be implemented after 30 days after the RMS approval	The applicability should be evalutated case by case
LT	Grouping Type IB national approval usually takes 30 days, but official variation approval can be announced 2 -3 weeks later Grouping Type II/IB national approval usually takes 30 days, but official variation approval can be announced 2-3 weeks later	
LU	2-3 months	
LV	RMS approval date = national approval date	It takes about 2-3 weeks to receive the national approval
NL	Usually RMS approval date = national approval date	Depends on the type of procedure, more complex procedures may have longer national phases; if PI impact: 1-3 months
NO	RMS approval date = national approval date	National approval is not granted for worksharing procedures unless texts are involved; if PI is impacted the national phase takes normally up to 3 months
PL	RMS approval date = national approval date	No national phase for manufacturing variations and variations with no PI impact; in case of changes to PI (ex. details of Batch Release site) or MA there is a nat. phase of approximately 4 months

PT	Can't be predictable	
RO	3-12 months	
SE	RMS approval date = national approval date	National approval is not granted for worksharing procedures unless texts are involved; if PI is impacted the national phase takes normally up to 3 months
SI	Grouping Type IB - once a WS is finalised, the approval letter is received within 1 month Grouping Type II/IB - once a WS is finalised, the approval letter is received within 2-3 months;	In case of changes to PI, the timeline may be up to 6 months, but the national authority can be notified to speed up the procedure
SK	Grouping Type IB - when WS is finalised, receipt of approval letter within 1-2 months Grouping Type II/IB - when WS is finalised, receipt of approval letter within 1-2 months	

Table 4 National Approvals

[adapted from an in-house survey for the European affiliates of a global pharmaceutical company [25]]

4.6.2 Post-approval Measures

After the national authorisations have been granted, the manufacturing site may implement the changes. In the best case, all approvals should have been issued in order for the manufacturing site to implement – provided that the products are all manufactured at the same site. If not all national approvals have been issued, a risk-based implementation may need to be executed.

If the manufacturing site intends to implement the changes as soon as possible, the applicant will need to ponder the risks of an implementation prior to the official national approval. According to the BPG Chapter 7, the MAH may implement the changes 30 days after the RMS-approval (implicit approval). [8]

In the event of commitments pendent to the procedure further variations may need to be submitted post-approval. This might be the case, if the reference product did not follow current ICH guidelines. However, this is always dependent on the particular procedure and will have to be discussed directly with the

respective procedure manager and/or assessor. Commitments may refer to the obligation of an applicant to submit a variation after completion of the worksharing.

5 Experiences of Different Applicants

5.1 The Questionnaire

In order to receive a feedback on the experiences of different pharmaceutical companies (applicants) with the harmonisation of the quality dossier an online questionnaire was created and then distributed with the aid of the German Pharmaceutical Industry Association (BPI). The questionnaire was prepared in German and later translated into English.

The questions were chosen based on practical experience in regulatory affairs and later agreed with the BPI regarding their suitability.

Closed multiple-choice questions were used to facilitate the evaluation of the results. They were also utilised to increase the probability of the respondents to answer the questions because it enables anonymity and makes it more difficult to deduce any company strategy. Of course, it should also not give the impression that this could be the goal of the survey.

The risk of multiple answers of the questionnaire from the same person or company was reduced by creating a cookie in the browser of the respondent and locking the session-id after completion. The respondents were also specifically asked not to respond more than once.

At the end of the questionnaire some basic information on the participating company was gathered in order to be able to compare the individual answers more precisely. These questions were not mandatory to not jeopardise the completion of the questionnaire.

Questions 4, 6, 8, and 9 were hidden if the company of the interviewee did not perform any worksharing procedures in the past (answer “None” in question 1). Question 10 was hidden if no consultation was conducted prior to worksharing and Question 14 was hidden if no Module 3 harmonisation was performed by the company.

The enquiries on general impression of worksharing and Module 3 harmonisation were presented to everyone because the interviewee may still have an opinion on the subject even if their company has not yet conducted the procedure.

Questions with an asterisk (*) are mandatory questions. If the final answer possibility of a question consists of “Other” or similar and multiple selections are possible, the participants were given a blank space to enter a response of their own.

“Other answers” were not altered (except for the correction of occasional spelling and grammatical errors).

The majority of the companies are located in Germany. But, also companies which have their headquarters either outside Germany and/or outside the EU participated. The size of the companies ranges from < 50 to > 50000 employees worldwide. In total, the questionnaire was sent to 70 pharmaceutical companies while giving a question period of about 4 weeks.

From these 70 companies 27 participated in the survey, equalling a participation rate of 38.6 %. As the sample size is inferior to 30, one probably cannot assume a standard distribution of the mean of the sampling distribution. However, one should still be able to evaluate tendencies within the results.

The number of participants for each individual question is stated in brackets. The different numbers stem from the fact that some questions were hidden to the interviewees. From a grand total of 27 only 2 participants did not finish all questions.

For questions 10 and 14 a graphical evaluation does not make sense because it was unanimous and thus no diagram is included.

5.2 Graphical Evaluation of the Results

(1) Approximately how many times has your company conducted worksharing (WS) since the entry into force of *Regulation (EC) No 1234/2008* (1 January 2010)?* (27)

a) None	13x
b) 1 – 10	7x
c) 11 – 20	4x
d) 21 – 50	2x
e) > 50	1x

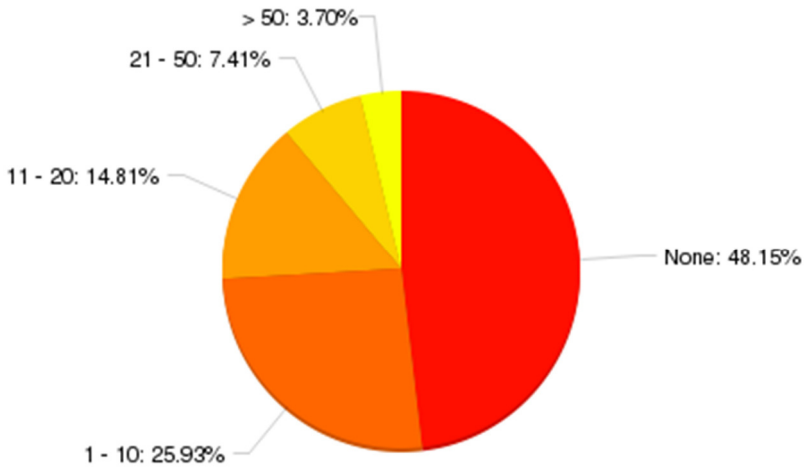

Figure 11 Question 1

(2) Why didn't you conduct any or why didn't you conduct more WS?* (27)

a)	Not yet (sufficiently) familiar with the procedure	3x
b)	Fear of restrictions	2x
c)	No need for harmonisation to date	9x
d)	Only centralised or predominantly centralised authorisations	2x
e)	Complex planning / preparation	10x
f)	Changes are only Type IA/IB, but worksharing follows the timeline of a Type II	7x
g)	Concern about too long a time frame	4x
h)	Not convinced of the advantages / had negative experiences	4x
i)	Other reasons	9x

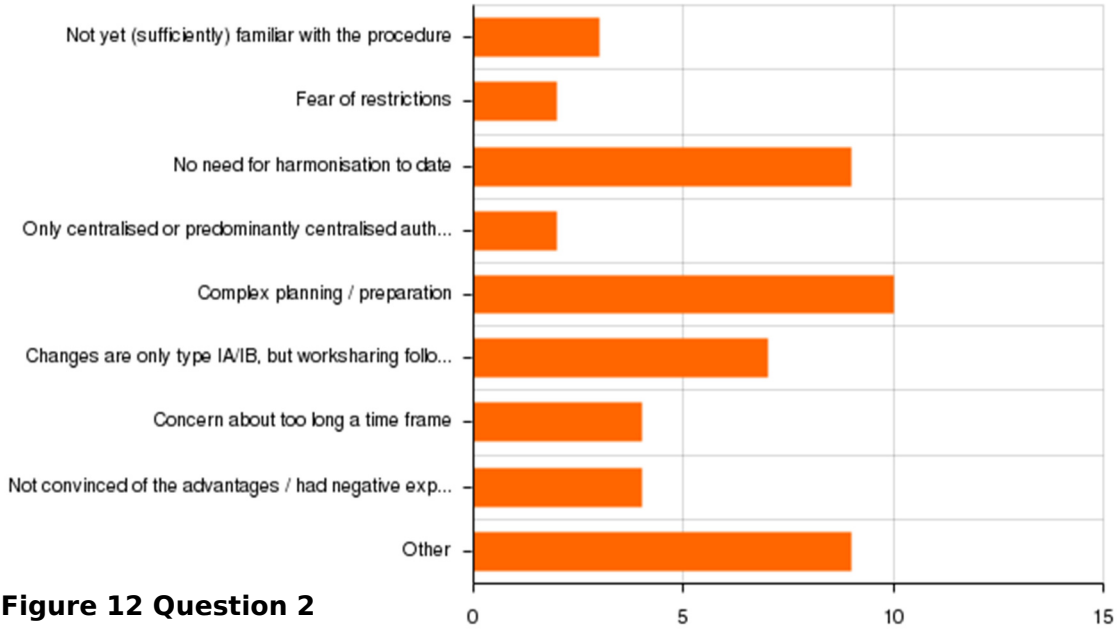

Figure 12 Question 2

Other answers included:

- Insufficient capacities
- Application for WS at the CMDh too costly (problem no longer exists)
- Mostly Type IA-variations
- Only license partner and not full responsibility of the authorisations, several DCPs with different MAHs in the CMS (competing companies)
- Various cases where WS procedure was not started after submission (not because of validation issues)
- Feedback from authorities that WS procedures are not desired for the PIL/SmPC
- Refusal of authorities to harmonise the current status in a single worksharing (harmonisation is only possible after an authorisation has been updated, thus requiring two consecutive procedures, which makes it unattractive, especially in terms of time)
- Only one product
- Not necessary because most products predominantly MRP/DCP

(3) Are (additional) worksharing procedures planned in the near future (1-2 years)? (25)

a) Yes 12x
b) No 13x

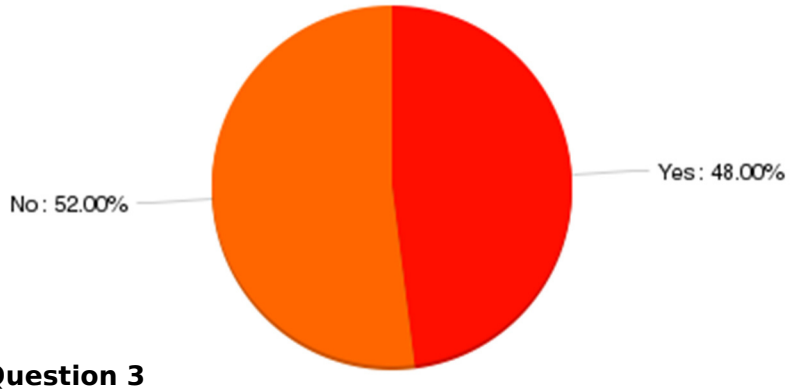

Figure 13 Question 3

(4) What types of changes were most often part of worksharing? (13)

a) Active substance 3x
b) Finished product 7x
c) Product information 2x
d) Other 1x

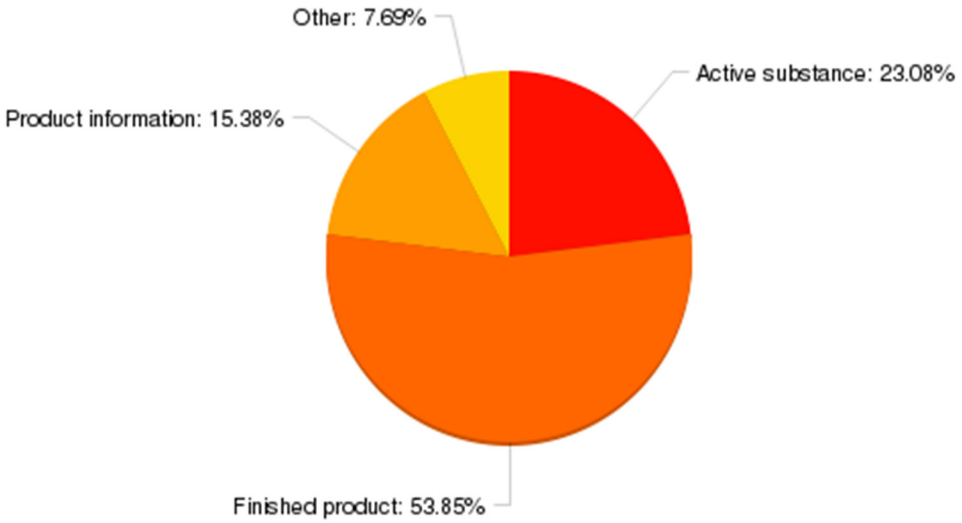

Figure 14 Question 4

(5) What advantages do you expect from worksharing or what advantages did you expect in advance?* (25)

a)	Saving of costs	6x
b)	Saving of time	8x
c)	Fewer comments from individual authorities	11x
d)	Harmonisation of the (national) marketing authorisations	19x
e)	Less effort / maintenance for marketing authorisations in the future	16x
f)	Faster approval of the variations in the WS	6x
g)	Reduction of the workload of the headquarters	3x
h)	Use of a known authority as RMS	9x
i)	Other advantages:	5x

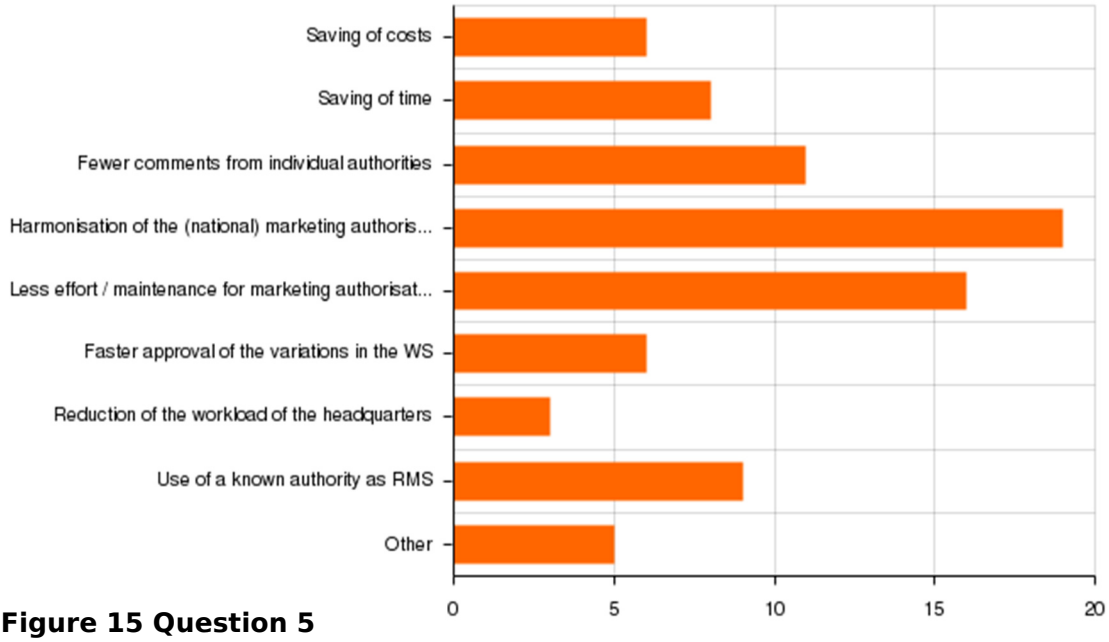

Figure 15 Question 5

Other answers included:

- None
- Can't be assessed
- Long-term saving of costs
- Long-term reduction of effort
- Harmonisation of the authorisations
- Uniform assessment of the changes / uniform outcome (2x)

(6) What advantages have you actually experienced?* (12)

a)	Saving of costs	3x
b)	Saving of time	3x
c)	Fewer comments from individual authorities	6x
d)	Harmonisation of the (national) marketing authorisations	10x
e)	Less effort / maintenance for marketing authorisations in the future	6x
f)	Faster approval of the variations in the WS	3x
g)	Reduction of the workload of the headquarters	4x
h)	Use of a known authority as RMS	7x
i)	Other advantages:	2x

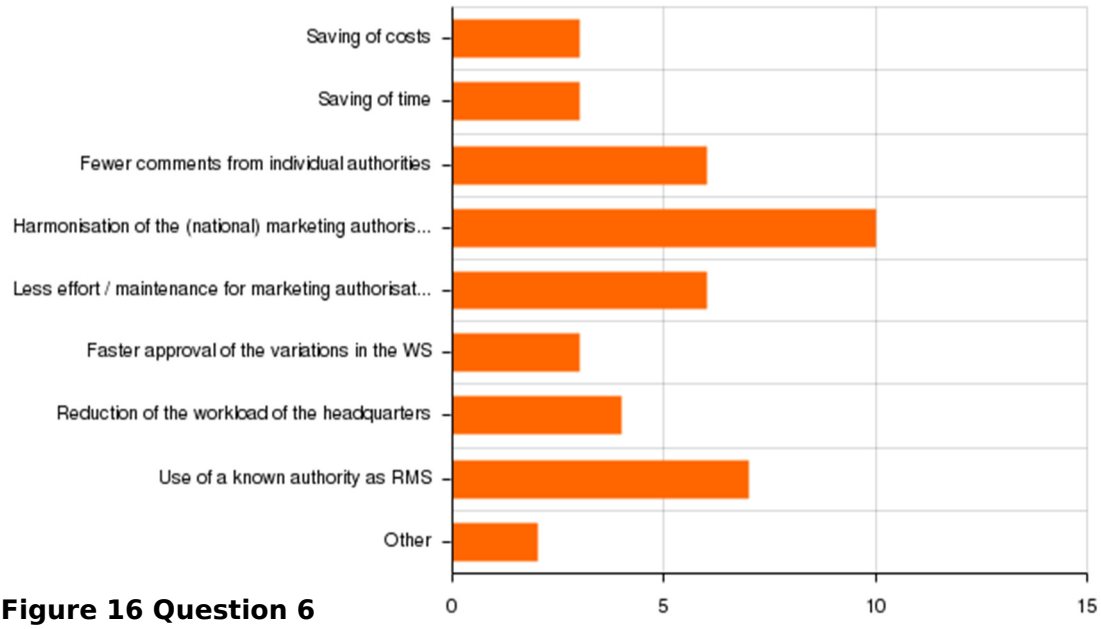

Figure 16 Question 6

Other answers included:

- Uniform assessment of the changes / uniform outcome (2x)
- Harmonisation of the authorisations
- Long-term reduction of effort

(7) What difficulties have you encountered so far before and during the procedure? (20)

a)	Comments from the authorities	3x
b)	Too long a time frame	2x
c)	Restrictions after approval	1x
d)	Complex planning / preparation	9x
e)	Other:	10x

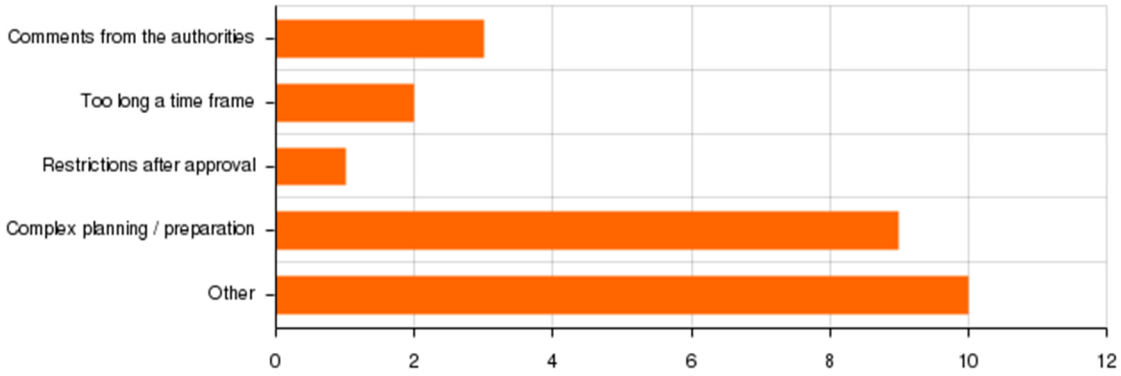

Figure 17 Question 7

Other answers included:

- None (3x)
- No previous experience / WS not yet conducted (6x)
- Various cases where WS procedure was not started after submission (not because of validation issues)
- Feedback from authorities that WS procedures are not desired for the PIL/SmPC
- Refusal of authorities to harmonise the current status in a single worksharing (harmonisation is only possible after an authorisation has been updated, thus requiring two consecutive procedures, which makes it unattractive, especially in terms of time)

(8) How high was the percentage of RMS = DE in worksharing conducted with purely national and/or MRP/DCP marketing authorisations?* (12)

a)	0 %	1x
b)	1 – 50 %	3x
c)	51 – 100 %	8x
d)	So far, no WS with national authorisations have been conducted.	-

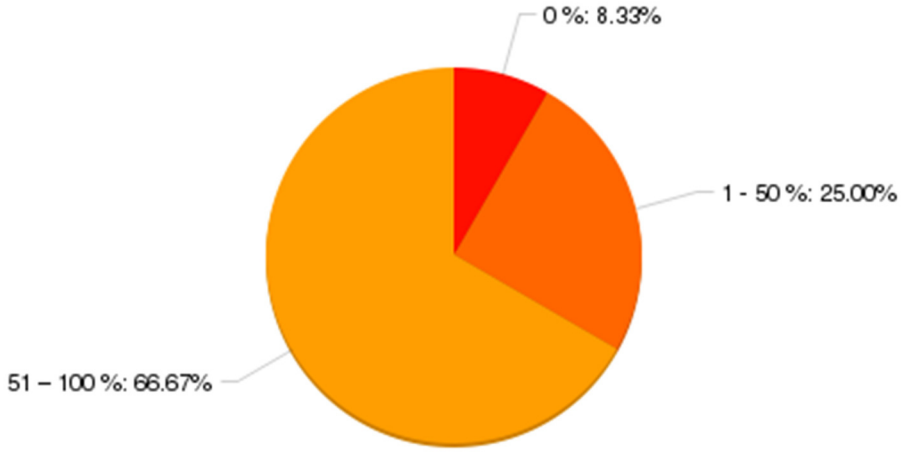

Figure 18 Question 8

(9) Did you take part in a consultation before worksharing (in writing or on-site)? (25)

a) Yes	1x
b) No	24x

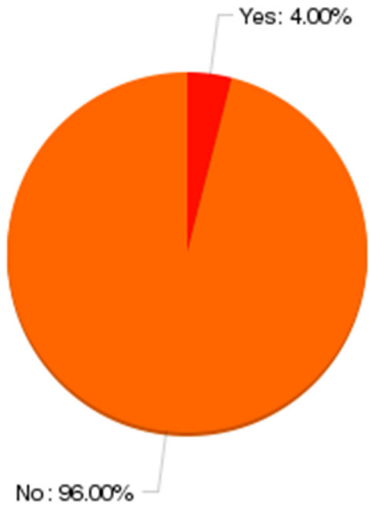

Figure 19 Question 9

(10) So, you have participated in at least one consultation. Where? (1)

a) At the BfArM	1x
b) At a different national competent authority	-
c) At the EMA	-
d) [Blank]	-

(11) What is your overall impression of worksharing?* (25)
Scale from 1 = very poor to 5 = very good, 0 = not assessable

	very poor (1)		rather poor (2)		neutral (3)		rather good (4)		very good (5)		not assessable (0)		
	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	Ø	±
Impression	-	-	-	-	2x	8,00	7x	28,00	6x	24,00	10x	4,27	0,70

Figure 20 Question 11

(12) Has your company previously carried out Module 3 harmonisations as WS (voluntarily or mandated)?* (25)

a)	Yes, 1 – 5	5x
b)	Yes, 6 – 10	1x
c)	Yes, 11 – 20	1x
d)	Yes, > 20	-
e)	No	18x

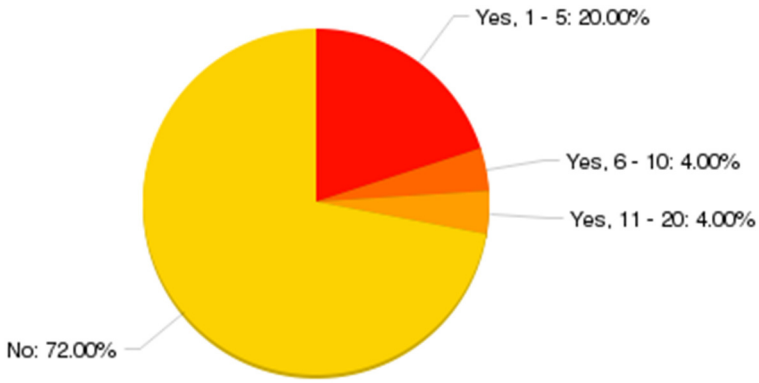

Figure 21 Question 12

(13) Why didn't you perform any or why didn't you perform more harmonisations of Module 3 by means of the worksharing procedure?* (25)

a)	Gap analysis showed problematic differences	9x
b)	Only centralised or predominantly centralised authorisations	1x
c)	Fear of restrictions	3x
d)	Complex planning / preparation	10x
e)	So far no or hardly any need for harmonisation of the quality dossier	12x
f)	Not yet (sufficiently) familiar with the procedure	3x
g)	Other reasons:	6x

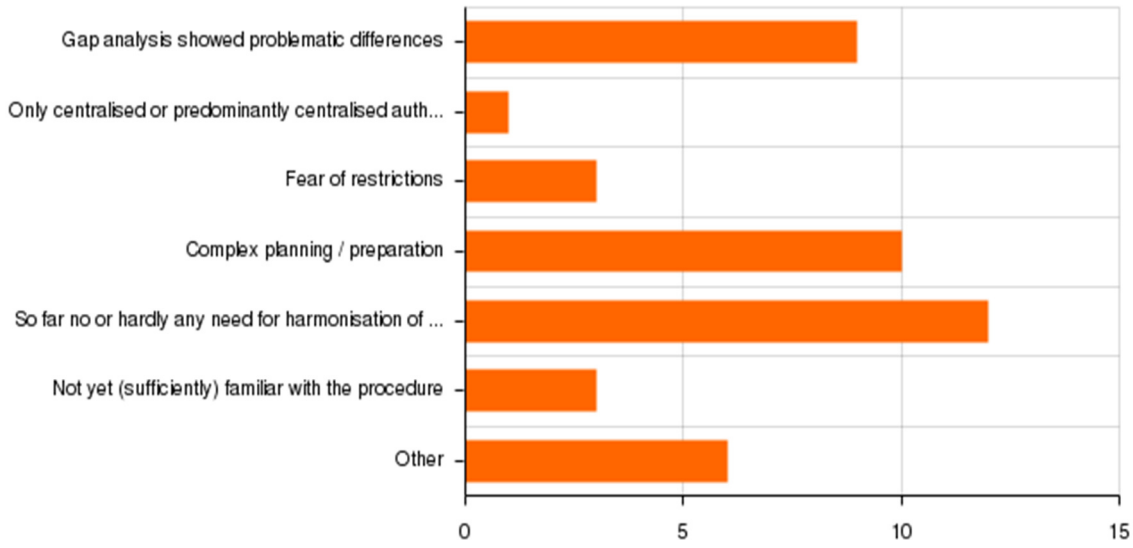

Figure 22 Question 13

Other answers included:

- Insufficient capacities
- Mostly Type IA-variations
- Licence partner
- Difficulty in stating the present/proposed situation and unclear how to do so in detail
- Different and contradictory feedback from the authorities in this respect
- Centrally authorised products

(14) On what grounds have you carried out harmonisations of Module 3?* (7)

a)	Voluntary	7x
b)	Mandated by an authority (e.g. after Union Referral)	-
c)	Both	-

(15) What is your overall impression of harmonisations of Module 3 by means of the worksharing procedure?* (25)
Scale from 1 = very bad to 5 = very good, 0 = not assessable

	very poor (1)		rather poor (2)		neutral (3)		rather good (4)		very good (5)		not assessable (0)		
	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	Ø	±
Impression	-	-	-	-	1x	4,00	2x	8,00	5x	20,00	17x	4,50	0,76

Figure 23 Question 15

(16) What suggestions do you have for improving worksharing in general?* (25)

a) More announcements / advice from the authorities 8x
b) Additional or more detailed guidelines 6x
c) Shortening of the procedural timelines 9x
d) Other: 10x

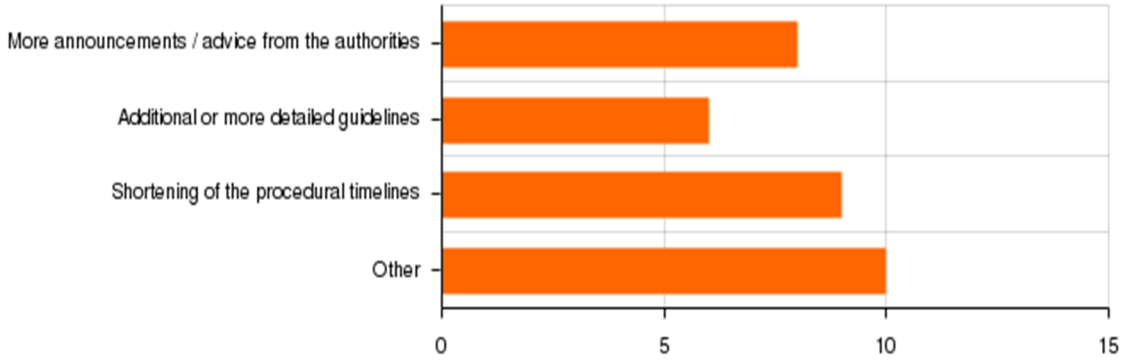

Figure 24 Question 16

Other answers included:

- None / no experience / not assessable (7x)
- Similar to the list of acceptable and not acceptable groupings, there should be overviews that show in which cases worksharing is beneficial or where WS are not possible
- In DE good / extensive information from the authorities, is this the same in other EU countries?
- More reliability at the start of the procedures (long delays are particularly problematic here as many products may be involved in the WS and then the implementation of the changes and all further planning for the products comes to a standstill)

Questions on basic information of the participating company

(17) Where is your company headquartered? (25)

a)	Germany	19x
b)	Outside Germany, but within the EU	4x
c)	Outside the EU	2x

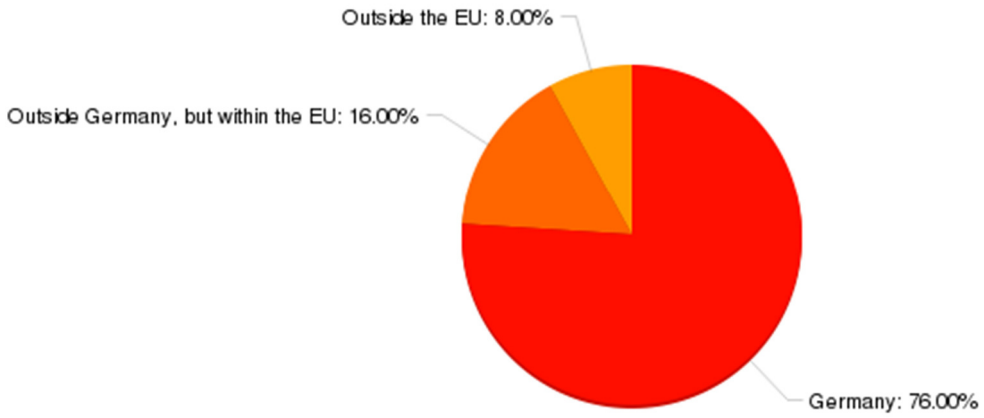

Figure 25 Question 17

(18) How many authorisations does your company hold in Germany? (purely national, MRP/DCP, CP; counting method: number of products including duplicates) (25)

a)	No own marketing authorisations in DE	2x
b)	1 -20	8x
c)	21 – 50	4x
d)	51 – 100	3x
e)	101 – 500	7x
f)	501 – 1000	1x
g)	1001 – 5000	-
h)	> 5000	-

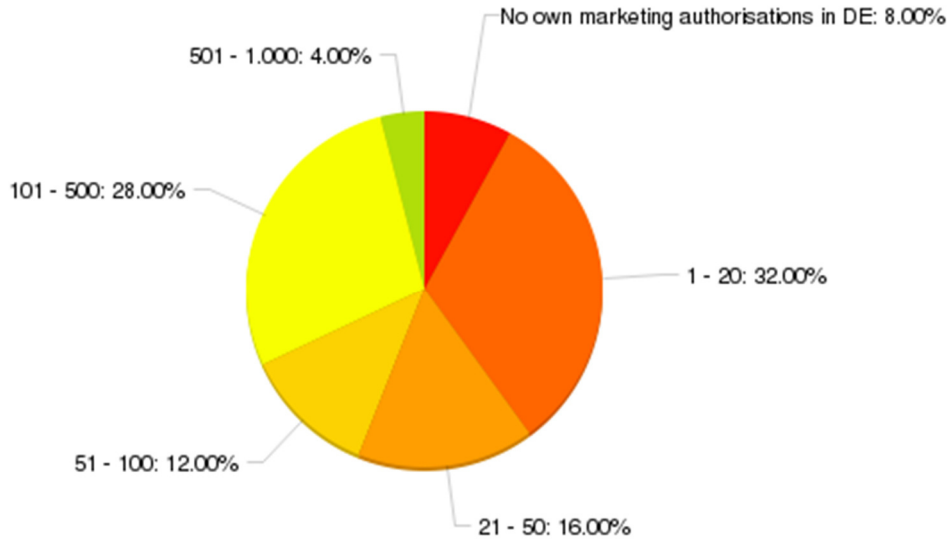

Figure 26 Question 18

(19) How many employees does your company (headquarters and affiliates) have worldwide? (24)

a)	< 50	5x
b)	50 – 200	2x
c)	201 – 1000	4x
d)	1001 – 5000	9x
e)	5001 – 10000	2x
f)	10001 – 50000	1x
g)	> 50000	1x

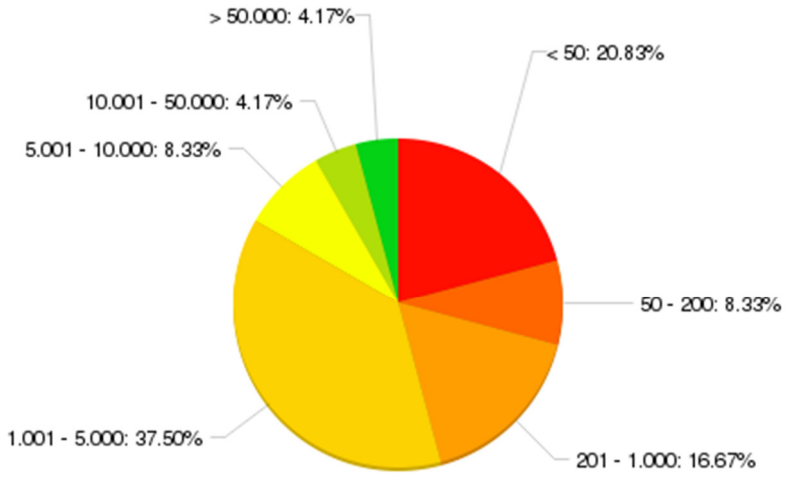

Figure 27 Question 19

[32]

5.3 Evaluation of Individual Responses

Looking at individual responses and considering questions 17-19, one can compare experiences of different types of companies. In order to do so, the answers were filtered by different company size, amount of marketing authorisations in Germany and by headquarter location.

5.3.1 Largest Companies

The biggest companies (from 5001 to > 50000 employees, 4 participants total) conducted worksharing a number of times ranging from none to between 21-50 with each graduation being represented exactly once (none, 1-10, 11-20 and 21-50). 50 % are planning further worksharing procedures in the near future. The changes that were most often part of worksharing are also distributed evenly (finished product, product information and other: 33.3 %), “other” likely being safety relevant changes. The most common reason why not more WS was conducted was that the changes were mostly Type IA/Type IB. Other reasons were mostly individual, e.g. various cases where WS procedures were not started at all.

Advantages mostly seen in this group were the harmonisation of the (national) marketing authorisations (100 %), fewer comments from authorities, less effort/maintenance for marketing authorisations in the future and the use of a known authority as RMS (all 66 %). Difficulties were mostly individual, including difficulties in procedure start, feedback by the authority that the WS procedure is not desired for PIL/SmPC and unwillingness of the authority to allow a single WS. The overall impression of worksharing is particularly high at 4.33 (out of a possible 5).

For the biggest companies, participation in Module 3 harmonisation is exactly 50 %. The difficulties were again mostly individual, including difficulty in stating the present/proposed situation for all different present statuses and having predominantly centrally authorised products. The overall impression of Module 3 harmonisation by means of the WS procedure is at exactly 5.00. It should be noted, however, that only one of the two firms in this group that took part in a harmonisation answered this question. The improvement suggestions are roughly evenly distributed among the possible answers and the individual field reads: “more reliability at the start of the procedures” (long

delays are problematic), which is consistent with the analogous question on WS in general.

5.3.2 Smallest Companies

Looking at the smallest participating companies (from < 50 to 200 employees, 7 participants total), only one company took part in at least one WS (1-10). The reasons why more WS have not been conducted were mostly the lack of a need for harmonisation to date (57.1 %). Other relevant reasons contain the circumstance that the changes were only Type IA/IB, complex planning/preparation and not yet being sufficiently familiar with the procedure. The additional field reads “license partner and not fully responsible” and “only one product”. The question if further WS are planned in the near future was answered with yes (28.6 %) and no (71.4 %). For the single company that conducted at least one WS the most relevant type of change was to the active substance.

The most common advantage was seen in the use of a known authority as RMS. Regarding the difficulties all choices were relevant, complex planning/preparation (40 %) being the most common one. The overall impression of WS is on average 3.50. 3 participants chose “not assessable” and the remaining 4 are distributed evenly among “neutral” and “rather good”.

In this group, 1 firm (< 50 employees worldwide) out of 7 had conducted at least one Module 3 harmonisation. The reasons that not more harmonisations have been performed range from problematic gap analysis, complex planning/preparation, but most importantly the lack of a need to consolidate the quality dossier (57.1 %). The overall impression of Module 3 harmonisation is on average 3.67. All fields in the answer possibilities are affected when it comes to improvement suggestions. However, the request for more announcements/advice from authorities is by far the highest (71.4 %) followed by the wish for additional or more detailed guidelines (42.9 %).

5.3.3 Medium Sized Companies

The bulk of the participants is found in the companies with a worldwide employee count of 201 – 5000 (13 participants total). 46.15 % have not conducted any WS before, the rest of 63.85 % has conducted 1-10, 11-20 or even 21-50 WS (7.69 %). Most answer options for not conducting any WS were

relevant, whereas complex planning/preparation rated the highest (46.2 %). The answer “not yet (sufficiently) familiar with the procedure” was not selected by anyone. Individual responses include “not enough capacities” or “not applicable”. The plan for more WS is almost aligned: yes (53.85 %) and no (46.15 %). Changes to the finished product were by far most often part of worksharing (71.4 %), whereas changes to the active substance and product information both rated 14.3 %.

All possible advantages that were stated were relevant to the participants, the most important being harmonisation of the (national) marketing authorisations (100 %), followed by fewer comments from the authorities, less effort/maintenance (both 57.1 %), faster approval of the variations in the WS and the use of a known authority as RMS (both 42.9 %). The most pertinent encountered difficulty was complex planning/preparation (50 %). 40 % of the participants stated “not applicable” and 10 % even specified that they did not experience any problems. The overall impression of worksharing is on average 4.71 which is even higher than the largest firms considered it. 38,46 % of the participants (5) chose “very good”. 2 participants chose “rather good” and 6 chose “not assessable”.

In this group of medium sized companies 4 out of 13 firms have previously carried out at least one Module 3 harmonisation (1-5: 15.4 %, 6-10: 7.7%, 11-20: 7.7 %). The most important reasons for not performing more harmonisations range from the lack of a need to harmonise (53.8 %), complex planning/preparation (46.2 %) to a gap analysis showing problematic differences (38.5 %). 2 participants (15.4 %) stated that they are not yet (sufficiently) familiar with the procedure. The overall impression of Module 3 harmonisation by means of the WS procedure is exactly 5.00, with 4 participants choosing “very good” and the rest choosing “not assessable”. Regarding the improvement suggestions, the most common answer was “shortening of the procedural timelines” (38.5 %). The rest was individual, mostly being “none” due to lack of experience. Another individual suggestion was to list advantageous and/or impossible worksharing similarly to the list of possible groupings.

5.3.4 Other Distinctions

Comparing the companies by their headquarters and looking at the differences, the results do not seem to vary substantially. About 50 % of both groups (based in Germany and based outside of Germany) have already conducted worksharing. The same goes for the question if further WS are planned

in the near future. For both groups the most common type of change is to the finished product. This aspect also applies to the question of the most important advantage, which is the harmonisation of the marketing authorisations. The experienced difficulties where mostly individual, however, while complex planning/preparation was either equally important or a close second. Interesting enough, the most common “other” difficulties for foreign companies were “no difficulties” and for companies based in Germany the most common answer was “n.a.” or “no past experience”.

Another difference is the percentage of RMS=DE. Germany-based companies have a percentage of 55.56 % in the “51-100 %” category and companies based elsewhere have a percentage of 100 %. Regarding a consultation prior to the WS, only one firm total took part in one (at the BfArM) and it is headquartered outside of Germany but within the EU.

The overall impression of WS is very similar (4.20 and 4.30), whereas the overall impression of the Module 3 harmonisation variant differs slightly (4.33 non-DE vs. 4.60 DE). The percentage of at least 1 conducted Module 3 harmonisation is also higher in Germany: 31.58 % vs. 16.67 % and also higher amounts of harmonisations have been performed. The most important reasons why not more alignments were performed was the lack of a need to harmonise (66.7 %) for non-DE and was more or less equally distributed among problematic gap analysis, complex planning/preparation and also the lack of a need to harmonise for DE.

Of course, as most participating firms are based in Germany (76 %), it is not clear if the gained results are applicable to most pharmaceutical companies outside of Germany.

As no participating company holds more than 1000 marketing authorisations in DE, one can distinguish between low amount (1 – 50) and high amount (51-1000) of marketing authorisations. Only two companies do not hold any authorisations in DE and it is unclear how many they hold worldwide. Therefore, they will be exempted from further analysis.

In the group with less authorisations considerably less companies have previously conducted at least one worksharing (54.55 % vs. 33.33 %) and no company has previously conducted more than 20 WS. 66.67 % are also not planning further WS in the near future. Regarding the reasons for not conducting more WS both groups share the most common reason which is “no need for harmonisation to date”. 25 % of companies with less authorisations in DE state that they are not yet (sufficiently) familiar with the procedure whereas no firm with more authorisations chose this answer. The changes

being mostly the subject of worksharing are very similar, changes to the finished product rating 50 % in both cases.

All advantages played a role for both groups, harmonisation of the authorisations turning out to be the most important one. The firms with more MAs were the only ones stating individual advantages. Among the specifically named answers, the planning/preparation aspect proved to be the most difficult, but for the companies with more MAs, the individual difficulties outweighed the others by far (60 %). When it comes to the RMS-ship, all companies with fewer MAs have a rate of 51-100 % of all previously conducted WS, whereas it lies at 66.7 % with the other group. Looking at the overall impression of WS, the average is very similar (4.14 vs. 4.33).

33.4 % of firms with fewer MAs in DE have conducted at least one WS, wheras 54.6 % of companies have done so with more MAs. When it comes to Module 3 harmonisations only 16.67 % of companies with fewer authorisations have ever conducted one (vs. 36.4 %). The most common reason for not conducting more consolidations is the lack of a need to harmonise for the firms with fewer MAs and complex planning/preparation for firms with more MAs. Again, the overall impression of Module 3 harmonisation by means of the WS procedure scores very similarly (4.50 vs. 4.33).

6 Discussion

6.1 Discussion of Results

As previously stated, the results can only show tendencies and the elicitation and participant's profiles need to be taken into account as well. Of course, the results cannot portray the situation in the entire European Union.

Most participants have completed the full survey once they started it (25/27 = 92.6 %). This shows that apparently the multiple-choice and anonymous approach was appropriate. One could also interpret an interest in the subject due to this fact.

The questions of the survey seem to be suitable overall to gather the experiences of the pharmaceutical industry about the procedure. This impression is underlined by the variance between the participants and the different results, especially the individual ones.

Looking at the graphical evaluation of all answers the participating companies are rather heterogenous, with company size ranging from < 50 to > 50000 employees and marketing authorisations in Germany ranging from none to 1000 MAs. Also, the headquarters of the individual companies differ, while Germany is still the most common location.

It can be observed that firms that have previously conducted worksharing in general and especially Module 3 harmonisations are not (yet) very prevalent (WS: 51.85 %, M3-Harmo: 28 %). Even among the companies that have never performed a WS only 1 (7.69 %) said that WS is planned in the near future. It should be noted, however, that worksharing is still a rather young procedure with WS being able to be conducted with purely national marketing authorisations is even younger (submitted as of 4 August 2013).

Still, for firms that have previously conducted at least one WS it is highly probable that they conduct further WS soon (91.7 %). As a consequence, one can ascertain notable loyalty to the procedure once it has been performed at least once.

When looking at all companies the reason "not yet (sufficiently) familiar with the procedure" for not conducting more worksharing is the second least common one. Other results are much more prevalent, i.e. the planning/preparation aspect and the lack of a harmonisation to date as well as individual

aspects. Still, about every ninth to eighth company states that they are not yet familiar with the procedures (11.11 % WS and 12 % M3 harmonisations). Nonetheless, it is noteworthy that all seven companies that have previously conducted at least one alignment of the quality dossier have all performed the voluntary version and not the one following a Union referral, which shows that they have dealt with this procedure on their own initiative.

What all firms have in common is that when they answered the question on overall impression of both worksharing and Module 3 harmonisations no one chose “rather poor” or “very poor”. In both cases the results are actually in between 4 (rather good) and 5 (very good). From this result one can deduce that most companies advocate the use of worksharing in general and in the case of Module 3 harmonisations in particular. Larger companies do this more than others, however, while medium sized companies generally rated highest in this regard.

As can be expected, larger companies and especially companies that hold more MAs, have conducted more WS and also plan more in the future. This observation is plausible because the more products or (national) marketing authorisations a company holds, the need for harmonisation should generally rise. But, this does not mean that small or medium sized companies do not conduct worksharing. In fact, one of the two companies that conducted an amount of WS between 21-50 since 2010 only has a worldwide employee count between 1001-5000 (the other having more than 50000).

Larger companies do not just have more experience with WS in general but have also encountered more individual difficulties. This also makes sense, as the more WS you have conducted, the more probable it becomes that you will encounter specific situations.

For smaller companies the complex planning/preparation aspect is the biggest difficulty encountered with worksharing. Interestingly enough, this is also true for companies which hold the most MAs. Even if that is the case it is probably due to different reasons: small companies state that they are lacking the resources to conduct more worksharing and especially more efficient worksharing while the firms with the greatest number of MAs most likely have a much higher workload regarding gap analysis and other pre-submission activities when dealing with their licenses. In that case it may be wise to schedule an advice procedure before application. As was observed in the questionnaire only one company has done so before (4 %).

Looking at the expected advantages vs. the advantages actually experienced the tendencies are comparable. In both questions the harmonisation of the

MAs was seen as the most important aspect. This is also arguably the most valuable asset of worksharing in general. The biggest deviation among expected advantages and encountered advantages was the “use of a known authority as RMS” (before: 36 %, after: 58.3 %) and “reduction of the workload of the headquarters” (before: 12 %, after: 33.3 %). That means, that for some companies, the advantages of the use of a known RMS and the reduction of HQ-workload were not expected to be that important, but later on turned out to be.

Regarding improvement suggestions the most important aspects for the interviewees was the shortening of the procedural timelines as well as the request for more advice from the authorities. Individual requests included the wish to have a similar list of possible worksharing as for possible groupings (compare Annex III of the *Variation Regulation*), more reliability at the start of the procedure and the wish for equally extensive information in other EU-countries as in Germany.

In general, answers between divergent firms do not differ substantially. The most differences can be seen between companies with more marketing authorisations vs. companies with less marketing authorisations.

6.2 Other Points to Consider

In addition to the topics presented in the questionnaire and discussed above there are other aspects to Module 3 harmonisation by means of the worksharing procedure that should be considered.

On one hand, numerous eCTD-sequences are required for the procedure and a lot of planning has to go into the meticulous gap analysis. Moreover, there is still only an approval if there is a unanimous consensus and the final outcome is likely influenced by the more restrictive opinions and/or more demanding national competent authorities.

On the other hand, the timetable of worksharing is exactly defined (30, 60, 90 days) and it is highly flexible due to many different scenarios where it could be used. It is a useful and unprecedented tool to facilitate and/or improve the level of harmonisation of established products and leads to a common dossier – which also facilitates the effort for audits and inspections by reducing the number of documents and providing a better overview of the contents of Module 3.

Furthermore, if the planning is mostly performed on HQ level, less resources are needed on affiliate level. A strategic choice of reference authority is possible and should therefore generate less comments from other Member States involved in the procedure.

On authority's side the prevention of duplication of work should be noted. The procedure also enhances the collaboration of different NCAs and may increase know-how on the subject for authorities that don't deal with Module 3 harmonisations very often. This could generally lead to quicker validation of procedures and perhaps even more guidance on the method.

Another point to consider is the fact that there won't be any classification issues in the validation phase of Module 3 harmonisations and thus less delay of procedure start as the classification of the alignment is already provided in the *Q&A-List for the submission of variations according to Commission Regulation (EC) 1234/2008* of the CMDh.

Regarding improvement suggestions on worksharing in general, in addition to the ones presented in the questionnaire, e.g. shortening of procedural timelines and more advice from authorities, *Medicines for Europe* also provided suggestions of their own.

Their proposals include an automatic validation of applications, allowing the applicant to justify a 30-day timetable with the letter of intent (for minor/non-complex WS), stopping the national phase of quality variations after the end of the procedure and even exclude national translations from the national phase, and lower procedural fees by introducing incentives. [6]

Especially the last two points could have a high impact on the overall acceptability of the procedure and thus increase the number of applications when looking at the answers from the questionnaire, but also the surveys on fees and national approvals from sections 4.3.3 and 4.6.1, respectively.

7 Conclusion

This thesis aimed to provide an overview on the topic of Module 3 harmonisation by means of the worksharing procedure. It was also meant to assess the execution and advocacy of the method and answer the question why not more worksharing is conducted by the pharmaceutical industry.

In order to address these topics, detailed legal background information on worksharing and Module 3 harmonisation was provided as well as guidance on the conduction of the method. The results of an online questionnaire presented the past experience with the procedure as well as the overall impression of worksharing and alignment of the quality dossier.

Through the display of the decision-making process, the different pre-submission tasks, the execution of the procedure itself and the post-authorisation activities, one can easily deduce that companies have to go through a considerable amount of planning in order to achieve an adequate result.

Although these tasks seem tedious at first, the risks are actually rather limited and the advantages outweigh the difficulties considerably.

This fact is further confirmed by the results of the questionnaire. None of the participating companies gave the worksharing procedure or the Module 3 harmonisation a bad rating and once performed at least once, it is highly probable that the firms will conduct further worksharing in the future.

It can therefore be concluded that the worksharing procedure is a viable way of conducting a Module 3 harmonisation and that the pharmaceutical industry generally favours its use, even if it is still a rather young procedure.

Advantages	Obstacles
Single evaluation and single outcome	Precise planning needed
Common dossier in all MS	Lack of experience due to young procedure
Less maintenance of MAs in the future	Almost no incentives for procedural fees
Strategic use of reference authority possible	Not possible to withdraw a single MS
Flexible procedure	Only approval if unanimous consensus
Few risks	
Predefined classification as a single Type II variation	

Table 5 Conclusion

7 Conclusion

The most important benefit of the procedure is undoubtedly the single harmonised outcome without the need of any prior or further consolidation. All the essential advantages and obstacles are again summarised in the table above (Table 5).

The findings in this thesis have contributed to the general understanding of the application for Module 3 harmonisation by means of worksharing and its execution. It undoubtedly helped to reveal the different obstacles applicants might face and the possibilities how they may overcome these obstacles.

The thesis may also have encouraged applicants to conduct more worksharing in the future, especially those companies that may not yet have conducted any at all.

Throughout the thesis different improvement suggestions were presented, especially by means of the questionnaire. Applicants as well as NCAs may find them helpful to tackle obstacles in the future.

Perhaps further research is needed to address the different possibilities to implement the recommendations and suggestions for improvement in order to further impact the numbers on started and finalised worksharing procedures.

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

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