Between Standardisation and Flexibility – Defining Granularity of the eCTD Module 3.2.S for Different Types of Drug Substances in Europe

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List of Abbreviations

Abbreviation	Term
AP	Applicant's Part (Open Part) of an ASMF
ASMF	Active Substance Master File
ATMP	Advanced Therapy Medicinal Product
CA	Competent Authority
CAT	Committee for Advanced Therapies
CEP	Certification of Suitability to the Monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CP	Centralised Procedure
CTD	Common Technical Document
CV	Controlled Vocabulary
DCP	Decentralised Procedure
eCTD	Electronic Common Technical Document
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
EU	European Union
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	In-process controls
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
NAS	New Active Substance
NCE	New Chemical Entity (new small molecule)
Ph. Eur.	European Pharmacopoeia
Q&A	Questions and Answers
RP	Restricted Part (Closed Part) of an ASMF
RPS	Regulated Product Submission
XML	Extensible Markup Language

Terminology Related to (e)CTD

In this thesis consistent terminology is used when relating to different items of the (e)CTD structure. The terms are defined as follows:

- Level: describes the hierarchical stage of an element, with highest level being the Modules and lowest level being the actual documents.
- Node extensions: are self-defined levels below headings, which can be used for sub-granularity in the eCTD
- Heading: is a defined and numbered CTD element, e.g. 3.2.S.1 or 3.2.S.2.5
- Section: includes the respective heading and all lower levels, as applicable
- Module: strictly speaking, "module" describes the 5 main CTD parts (see Figure 1). In deviation from that terminology, in this thesis also "Module 3.2.S" and "Module 3.2.P" are used, which include heading 3.2.S/3.2.P itself and all substructures (see Chapter 2.2).

eCTD lifecycle operators and lifecycle operations are written in capital letters, i.e. NEW, REPLACE, DELETE, APPEND.

1 Introduction and Scope

Apart from data on safety and efficacy, information on the quality of the medicinal product is the basis of any Marketing Authorisation Dossier. An important part of the quality documentation will be information on the quality of the drug substance being the actual active component of the product. However, drug substances show a vast variety in terms of their nature, chemical structure, origin, manufacture, etc., ranging from simple sodium chloride to complex tissue-engineered products. Naturally, the amount of available data on their quality will vary to almost the same extent.

Nevertheless, fundamental principles on the content of their drug substance quality information, as laid down in Directive 2001/83/EC and supplemented by numerous Guidance documents, apply to every drug substance.

As a harmonised structure for the organisation of documentation in the MA dossier, the Common Technical Document format (CTD) has been agreed at ICH level and subsequently implemented in the ICH regions. The granularity of the CTD i.e. the organisation and placement of the documents in the dossier is described in ICH Guideline M4(R3) which recently underwent revision. The electronic version of the CTD, the current eCTD v3.2.2, has become the widely accepted submission standard for MA dossiers in the EU and the ICH regions. The content of the quality documentation (CTD Module 3) in particular is covered in ICH Guideline M4Q.

eCTD format is widely used, remarkably independent from the type of drug substance, because it apparently offers both a standardised structure of documentation and basic flexibility to adapt to the individual volume of information for the respective drug substance in Module 3.2.S.

This master thesis will discuss how the legal requirements on the documentation for drug substance quality are to be structured in accordance with the granularity requirements for the (e)CTD. The differences for Small Molecules and Biotech products and consequent implications on dossier organisation will be analysed. In addition, strategies for planning of the MA dossier and defining granularity with regard to the type of drug substance will be described.

Furthermore, it will be analysed if the currently required eCTD granularity is appropriate for the different drug substance parts and if identified issues have been solved by the recent revision of ICH Guideline M4.

Finally, this thesis will look at the situation in the drug product excipients section of the eCTD and, ultimately, briefly address the potential for improvement with the advancing eCTD v4.0 specification.

2 CTD Guidance and Granularity Document

2.1 Common Technical Document (CTD)

The Common Technical Document (CTD) is the common standard format for the presentation of data on drug products in the ICH regions. This format has been agreed by the ICH members and is laid down in the ICH M4 Guidelines [1].

The granularity of the CTD, i.e. the organisation and placement of documents in the dossier, is described in ICH Guideline M4(R3) [2], which has been revised recently[1]. The Common Technical Document is organised modularly. Module 1 is region specific while Modules 2, 3, 4, and 5 are common for all ICH regions. Modules 3, 4, and 5 contain detailed descriptions, data, reports etc., which are summarised in Module 2, as shown in the "CTD triangle" below:

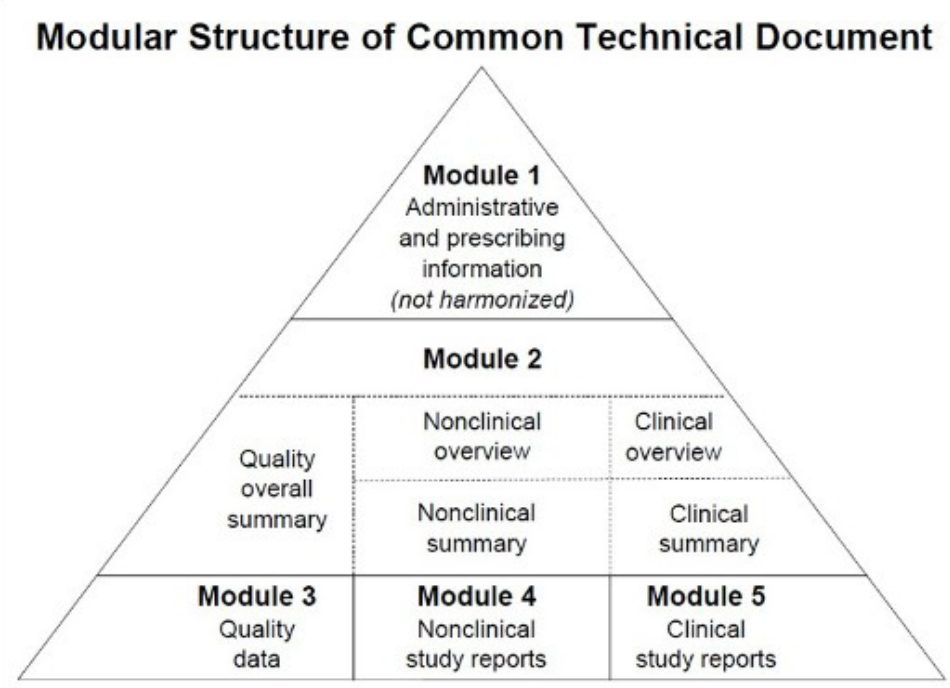

Figure 1: The CTD Triangle

The documentation relating to the quality of drug substance and drug product is located in Module 3. This Module's principle content and structure is laid down in ICH Guideline M4Q [3].

The actual data is contained in Module 3.2.S for the drug substance and 3.2.P for the drug product. Module 3.2.S can be multiplied in case of multiple drug substances or multiple drug substance manufacturers. Accordingly, multiple Module 3.2.P are possible in case of multiple pharmaceutical forms and/or strengths for the drug product and/or multiple manufacturers.

[1] Remark: The revision process is almost completed, but not yet finally approved and published at ICH. Basis for this thesis is the final version dated 01 March 2016.

2.2 Structure and Contents of Module 3.2.S

Scope of this thesis is the granularity of (e)CTD Module 3.2.S. This Module is structured into seven main headings and several sub-headings as follows:

3.2.S.1 General Information
- 3.2.S.1.1 Nomenclature
- 3.2.S.1.2 Structure
- 3.2.S.1.3 General Properties

3.2.S.2 Manufacture
- 3.2.S.2.1 Manufacturer(s)
- 3.2.S.2.2 Description of Manufacturing Process and Process Controls
- 3.2.S.2.3 Control of Materials
- 3.2.S.2.4 Controls of Critical Steps and Intermediates
- 3.2.S.2.5 Process Validation and/or Evaluation
- 3.2.S.2.6 Manufacturing Process Development

3.2.S.3 Characterisation
- 3.2.S.3.1 Elucidation of Structure and other Characteristics
- 3.2.S.3.2 Impurities

3.2.S.4 Control of Drug Substance
- 3.2.S.4.1 Specification
- 3.2.S.4.2 Analytical Procedures
- 3.2.S.4.3 Validation of Analytical Procedures
- 3.2.S.4.4 Batch Analyses
- 3.2.S.4.5 Justification of Specification

3.2.S.5 Reference Standards or Materials

3.2.S.6 Container Closure System

3.2.S.7 Stability
- 3.2.S.7.1 Stability Summary and Conclusions
- 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
- 3.2.S.7.3 Stability Data

ICH Guideline M4Q provides general information and gives examples on which kind of quality data should be presented under each heading. In that guideline, basic differences between documentation requirements for Biotech products and chemical (Small Molecules) drug substances are already addressed.

2.3 Electronic Common Technical Document (eCTD)

The eCTD is the approach to create a standard for electronic transfer of regulatory information organised in the CTD structure, which was developed by the ICH M2 Expert Working Group [4]. The current eCTD specification v3.2.2 (now handled under ICH topic M8) has finally been approved in July 2008.

The introductory section of the specification document defines the eCTD "as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission." The specification document further points out that the eCTD should be "applicable to all modules of initial registration applications and for other

submissions of information throughout the life cycle of the product, such as variations and amendments."

The ICH eCTD specification only covers the common CTD Modules 2 to 5, however, the opportunity to link to regional Module 1 is given.

The eCTD organises the CTD content by using an XML backbone, which covers the entire submission including all hierarchical levels and includes references to each individual file. The XML backbone allows for navigation throughout the CTD and for use of meta-data for the entire submission and each document within the submission. The XML backbone is described in detail in Appendix 6 of the eCTD specification. The actual content files are organised in dedicated Module folders by defined folder and filenames as described in detail in Appendix 4 of the specification.

Some CTD sections are repeatable. In order to handle multiple sections in the eCTD correctly, additional attributes are assigned to them. Amongst others, this applies to Module 3.2.S, which can be multiplied in case of multiple drug substances and/or manufacturers. Attributes for "Drug Substance Name" and "Manufacturer" must be assigned to each Module 3.2.S, allowing identification of the respective information contained thereunder.

An important advantage of using the eCTD is the benefit for dossier maintenance and document lifecycle. Supplements to the original contents, e.g. responses or variations, can be submitted incrementally while preserving the previous documents. Meta-data included in the XML backbone aids in identification of the updated content. These incremental updates are called sequences.

Lifecycle changes are implemented in the dossier by addition of new documents or modification or deletion of previously submitted ones. In the eCTD specification, the corresponding lifecycle operations NEW, REPLACE, and DELETE are defined. The fourth operation APPEND, with which a new document could be attached to an existing one, is not recommended to be used in the EU [5].

eCTD v4.0

For quite a long time, discussion about a fundamental revision of the eCTD specification built on the Regulated Product Submissions concept are ongoing, aiming to build the Next Major Version eCTD v4.0; a brief overview of the specification and the current status is provided in see Chapter 10.

2.4 The Granularity Document

The Annex to ICH Guideline M4 is known as the "Granularity Document" [2]. The Granularity Document outlines the basic principles on how an (e)CTD should be organised. The last revision, R3, of the Annex had been agreed in January 2004. It has been adopted in the EU by the Committee of Human Medicinal Products (CHMP) in February 2004 in Guideline CPMP/ICH/2887/99.

According to ICH Guideline M4, "document" in the eCTD equals a single file. With few exemptions, only pdf format is accepted for these files. The Granularity Documents gives strict guidance at which headings documents should be located, i.e. how the dossier should be granulated.

Taken from the current version of the Granularity Document, Table 1 lists those levels in the eCTD hierarchy at which files should be placed in 3.2.S.

Table 1: Granularity of Module 3.2.S [2]

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 Manuf. Process and 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*
		3.2.S.2.6 Manufacturing Process Development
	3.2.S.3 Characterisation	3.2.S.3.1 Elucidation of Structure*
		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*	
	3.2.S.6 Container*	
	3.2.S.7 Stability	3.2.S.7.1 Stability Summary and Conclusions
		3.2.S.7.2 Post-approval Stability*
		3.2.S.7.3 Stability Data
*abbreviated section title		
Key		
Documents rolled up to this level are not considered appropriate		
One or multiple documents can be submitted at this level		

Recently, the Granularity Document underwent revision (see Chapter 8). This thesis will analyse if current requirements from the Granularity Document for Module 3.2.S granularity are appropriate for different types of drug substances. In the second step, it will check whether the revised version could improve the suitability for eCTDs in the currently valid specification v3.2.2.

In addition, updates to the Granularity Document in the course of the introduction of eCTD 4.0 will be discussed, analysing whether they could improve dossier organisation for different drug substances (see Chapter 10).

3 Overview on Types of Drug Substances

Dependent on their nature or origin, drug substances can be roughly grouped into different types, e.g. chemicals, herbals, biologicals, tissues and so on. This thesis will put the focus on the most common types of drug substance including Small Molecules (chemical drug substances) and Biotech products.

For the pharmacologically active component of a medicinal product, different common terms are used. EU guidelines and legal documents usually use "active substance" or "active pharmaceutical ingredient", whereas the ICH guidelines use "drug substance". Because "drug substance" is also the term in the CTD specification, which is the main focus of this thesis, that term will be consistently used herein.

3.1 Small Molecules

Most approved drug substances in the EU are Small Molecules. These substances have a relatively low molecular mass of usually less than ~1000 Da and are chemically and physically well defined [6]. They usually bind to one or few specific target structures where their pharmacological action takes place by altering the activity of these targets. Due to their low molecular mass, they can relatively easily diffuse across cell membranes and act inside the cells.

Almost all Small Molecules are manufactured by full- or semi-chemical synthesis. Such manufacturing processes can be well characterised and monitored, what usually results in high product purity and general in constant quality. Therefore, quality of the drug substance can be usually determined by control of the final product.

3.2 Biotech Products

Biotech products are much larger and complex compounds than Small Molecules and of biological origin. For the purpose of this thesis, the drug substance type Biotech products is comprised of Biologicals and Advanced Therapy Medicinal Products (ATMPs) which are described further in the following Chapters,

3.2.1 Biologicals

In the EU, Biologicals are legally defined in the Annex 1 of Directive 2001/83/EC, as medicinal products "the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control." [7] Medicinal products derived from human blood and human plasma, immunological medicinal products, and ATMPs and their respective drug substances are covered by this definition as well. In this thesis, however, mainly recombinant proteins are discussed as representative members for Biologicals.

The vast majority of Biologicals for which an MAA is filed, are proteins manufactured by complex biotechnological processes like recombinant DNA method, such as therapeutic antibodies, growth factors or components of vaccines. From their physicochemical properties, these drug substances have molecular weights of usually (much) more than 10,000 Da.

They show very complex structures, with secondary and tertiary formations. Furthermore, during the manufacturing process they usually undergo further modifications like glycosylation. Therefore, understanding and controlling the manufacturing process is essential for ensuring uniform quality of both Biologicals drug substance and product.

3.2.2 Advanced Therapy Medicinal Products (ATMPs)

ATMPs are legally defined in Article 2 of the ATMP Regulation (EC) 1394/2007 [8], with references to Part IV of Annex I to Directive 2001/83/EC [7]. Roughly, they comprise gene therapy products, somatic cell therapy products and tissue engineered products. Common tissue preparations or non-manipulated cells do not fall under this ATMP definition.

Compared to Biologicals, ATMPs are even more complex as they consist of numerous components for example a virus particle plus nucleic acid, whole cells, or even entire tissues. At that point, differentiation between medicinal product as a whole and the actual drug substance becomes virtually impossible.

It is obvious, that physicochemical methods can only make up for a very limited part of ATMP characterisation and control. Again, controlling the quality of these products highly depends on understanding and control of the manufacturing process.

4 Small Molecules

4.1 Regulatory Aspects in the EU

Small Molecules are the most common type of drug substances and many of them already have a long history of use in medicine. They are what is commonly referred to as "drugs". Compared to Biologicals or even ATMPs, they have a very simple chemical structure allowing for easy characterisation by standard methods. Nevertheless, these substances must fulfil a number of requirements as detailed in various guidance documents.

Due to their simple structure and the manufacture by reproducible chemical synthesis processes, substance quality is not inevitably linked to the manufacturing process but can be determined by unambiguous physicochemical testing of the final product. This allows for manufacturing at multiple sites by multiple manufacturers, without deviation from defined drug substance specification. Hence, development of the medicinal product and manufacturing of the drug substance can be performed independently from each other. In fact, it is quite usual for many products with a Small Molecule drug substance, to include drug substance documentation from two or more manufacturers in the eCTD, i.e. multiple Modules 3.2.S (see Chapter 2.3).

For an MAA for a Small Molecule as a New Active Substance (NAS), in general all three regulatory pathways are acceptable in the EU, i.e. the National, the Decentralised (DCP), or the Centralised Procedure (CP). However, the CP will be mandatory for NAS for which the therapeutic indication is the treatment of any of the following diseases: AIDS, cancer, neurodegenerative disorder, diabetes, auto-immune diseases, or viral diseases [9]; or in case they are orphan medicinal products pursuant to Regulation (EC) No 141/2000 [10].

4.1.1 New Active Substance vs. New Chemical Entity

NAS status is attributed to any substances that have not been approved as active substance in a medicine in any indication anywhere in the EU. For NAS, documentation requirements are potentially more extensive, as no previous experience with the substances exists. NAS status can also apply to Biologicals and ATMPs; however, their Module 3.2.S will have a big volume anyhow why NAS status makes no difference in this regard (see Chapter 5.2).

New Chemical Entity (NCE) is an ICH term and refers to new Small Molecules being used as drug substance in medicinal products for the first time in general.

For NCEs like for NAS, the full set of documentation must be submitted in Module 3.2.S. For many NCEs, the new drug substance is developed by the MAA Applicant or at least in close collaboration with them. Therefore, the details on the manufacture process and further proprietary information are usually disclosed to the Applicant, even if the actual drug substance manufacturer is a third party. In the eCTD, usually just one Module 3.2.S is submitted containing the entire data on the drug substance.

4.1.2 Active Substance Master File (ASMF)

However, the drug substance documentation can also be submitted and assessed separately from the MA dossier for the product. In Europe, the Active Substance Master File (ASMF) procedure exists for this purpose. This procedure can be followed for "well-defined active substances" (including NCEs) only, as laid down in Annex 1 of Directive 2001/83/EC [7].

In principle, the drug substance manufacturer (called the ASMF Holder) prepares a dossier (called the ASMF) in CTD format, containing the full information on the drug substance. Exact details on the organisation of the ASMF are described in EMA ASMF Guideline CHMP/QWP/227/02 Rev. 3 [11]:

> *"The scientific information in the ASMF should be physically divided into two separate parts, namely the Applicant's Part (AP) and the Restricted Part (RP). The AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the ASMF holder regards as confidential, see Annex 1. (..] In all cases the AP should contain sufficient information to enable the Applicant/MA holder to take full responsibility for an evaluation of the suitability of the specification for the active substance to control the quality of this active substance for use in the manufacture of a specified medicinal product. "*

When using an ASMF, the Applicant incorporates the AP of the ASMF as provided from the ASMF holder into eCTD Module 3.2.S of the MA dossier. The ASMF documents may be supplemented by information from the dug product manufacturer, for example concerning control of the drug substance at the drug product manufacturer.

The confidential information in the RP usually relates to details of the drug substance manufacturing process. Annex 1 of the ASMF Guideline lists the documents of Module 3.2.S, which are expected to be in the AP and the RP, respectively, as shown below:

Table 2: Overview on ASMF Contents [11]

Table 1	CTD format	Applicant's Part	Restricted Part
3.2.S.1	General information	x	
3.2.S.1.1	Nomenclature	x	
3.2.S.1.2	Structure	x	
3.2.S.1.3	General properties	x	
3.2.S.2	Manufacture	x	X
3.2.S.2.1	Manufacturer(s)[2]	x	
3.2.S.2.2	Description of Manufacturing Process and Process controls	a)	b)
3.2.S.2.3	Control of Materials		X
3.2.S.2.4	Control of critical steps and intermediates	c)	d)
3.2.S.2.5	Process validation and/or Evaluation		X
3.2.S.2.6	Manufacturing Process Development		X
3.2.S.3	Characterisation	x	
3.2.S.3.1	Elucidation of Structure and other Characteristics	x	
3.2.S.3.2	Impurities	x	e)
3.2.S.4	Control of Drug Substance	x	
3.2.S.4.1	Specification	x	
3.2.S.4.2	Analytical procedures	x	
3.2.S.4.3	Validation of analytical procedures	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.4.5	Justification of specification	x	f)
3.2.S.5	Reference standards or materials	x	
3.2.S.6	Container Closure System	x	
3.2.S.7	Stability	x	
3.2.S.7.1	Stability summary and conclusion	x	
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	x	
3.2.S.7.3	Stability data	x	

a) Flow chart and short description is regarded as sufficient, if detailed information is presented in the Restricted Part. However, full validation data on the sterilisation process may be requested in the Applicant's Part (in cases where there is no further sterilisation of the final product).

b) Detailed information.

c) As far as the information is also relevant for the Applicant/MA holder.

d) As far as the information is related to the detailed description of the manufacturing process and as far as this information is not relevant for the Applicant/MA holder.

e) In so far as the information is related to the detailed description of the manufacturing process and in so far as the ASMF holder sufficiently justifies that there is no need to control these impurities in the final active substance.

f) As far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

4.1.3 Certification of Suitability (CEP)

A large number of substances having been used for longer time in pharmaceutical context are monographed in the European Pharmacopeia (Ph. Eur.). Referencing to a Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) for the drug substance is another (abridged) way to provide data on drug substance quality in the eCTD.

Briefly, a CEP confirms that the quality of a substance is in line with the Ph. Eur. specifications. CEPs are issued upon application by the substance manufacturer at the Certification Secretariat of the European Directorate for the Quality of Medicines (EDQM). The CEP procedure is laid down in Resolution AP-CSP (07)1, adopted by the Public Health Committee of the Council of Europe [12].

According to this resolution, the CEP procedure

> *"is intended to be used for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the European Pharmacopoeia Commission:*
>
> - *organic or inorganic substances (active or excipients), manufactured or extracted.*
> - *substances produced by fermentation as indirect gene products, which are metabolites of microorganisms, irrespective of whether or not the microorganisms have been modified by traditional procedures or r-DNA technology (see the monograph Products of Fermentation).*
> - *products with risk of transmitting agents of animal spongiform encephalopathies (TSE) (see the monograph Products with risk of transmitting agents of animal spongiform encephalopathies).*
>
> *The procedure will not be applicable for direct gene products (proteins), products obtained from human tissues, vaccines and blood products and preparations"*

Hence, Biologicals and ATMPs as defined in this thesis are excluded from CEP. For obvious reason, NCEs are never compendial, thus CEPs are not available,

4.2 Implications for the Granularity of Module 3.2.S

For many well-known Small Molecules, documentation from more than one manufacturer is submitted with the MA dossier. In such case, a separate Module 3.2.S is recommended for each manufacturer's documents (see Chapter 2.3). Nevertheless, it is also possible to submit documentation in a common Module 3.2.S that covers multiple manufacturers if their documentation, in particular manufacturing process and specification, is largely identical.

In analogy, for products containing more than one drug substances, a separate Module 3.2.S for each drug substance is mandatory.

4.2.1 New Chemical Entities

For an NCE usually only one manufacturer is initially included in the MA dossier, who was very often directly involved in development of drug substance and product. Only limited information on the drug substance is available from other sources, like e.g. experience with similar substances from the scientific literature. Therefore, the Applicant will need to include elaborate data on every aspect of the drug substance particularly with focus on identification, development & manufacture, and control [13].

(1) Identification: Inherently, the chemical structure of an NCE had not been established thoroughly before development of the product. Therefore, substantial data on the drug substance and potential related substances must be generated by the manufacturer. The related documentation should be provided under eCTD headings 3.2.S.3.1 and 3.2.S.3.2. In case of extensive

characterisation studies, respective reports should be included in these sections as well. In addition, information extracted from studies on structure and properties could be presented under headings 3.2.S.1.2 and 3.2.S.1.3. Justifications for certain impurity limits should be discussed under heading 3.2.S.4.5. Additional reports relevant for implementation of reference standard could also be provided under heading 3.2.S.5, if applicable.

(2) Development & manufacture: Developing an NCE from discovery to the final medicinal product is a long process. Over time, knowledge about the substance grows, as do requirements on drug substance quality for conduct of clinical studies in ever-larger patient populations. Very likely, the manufacturing process will be optimised and specifications will be modified during that time, resulting in substance batches, which may show differences in quality between early and late batches. Comparability of early and late batches must be evaluated and demonstrated to justify that results from early (pre-)clinical studies using early batches are comparable to later studies' results and hence still relevant for the MAA.

A reproducible manufacturing process including definition of steps and of in-process controls (IPC) and parameters must have been established and validated at the time of MAA submission. Development reports and related data should be included especially under headings 3.2.S.2.3, 3.2.S.2.4, 3.2.S.2.5, and 3.2.S.2.6.

(3) Control of drug substance: For the NCE, a specification must be defined, which is based on the knowledge gained during manufacturing process development and substance characterisation. The development involves establishment and refinement of analytical methods and their validation. The generated information on these procedures should be included under heading 3.2.S.4.2 whereas respective validation reports will be placed under 3.2.S.4.3.

Since the aspects discussed above are closely related, none can be thoroughly addressed without looking at the others. Submission of a Control Strategy Summary document could be considered to illustrate the overall development concept (see Chapter 5.3).

The generated information will be usually available as descriptive documents (e.g. for methods) or reports (e.g. for method validation, characterisation exercises, or developmental or comparability studies). It is the Applicant's decision whether these additional data are incorporated into a single document or are provided as multiple documents under the respective eCTD heading. In general, either approach is in line with the Granularity Document (see Chapter 2.4). Chapter 6 will discuss considerations the Applicant should make to come to a decision for the granularity of Module 3.2.S.

Submission of an ASMF (Chapter 4.1.2) for an NCE is permitted. However, this would not reduce the overall volume of information required in Module 3.2.S.

4.2.2 Well-known Small Molecules

For well-known or even compendial Small Molecules without CEP use, usually just one document per lowest heading as outlined in the Granularity Document (see Chapter 2.4) is appropriate. More than one document could be possible for detailed descriptions of analytical methods and/or their validation, or for documents containing information that are likely to be modified in future (see Chapter 6.2.2).

4.2.3 ASMFs and CEPs

When the Module 3.2.S of the MA dossier is supported by an ASMF, the Applicant must incorporate the Applicant's Part into the dossier, as provided by the ASMF holder. Of course, the information from the Restricted Part will be missing in the AP. Instead, brief references from the documents in AP to the RP should be provided stating that this information can be found in the RP.

The ASMF holder should provide the ASMF in eCTD format directly to the Competent Authority. Depending on whether the substance is an NAS or well known, granularity and contents considerations from Chapters 4.2.1 or 4.2.2, respectively, are applicable. The Applicant should "include a copy of the AP" [11] in the MA dossier, i.e. should not change granularity.

In addition to the analytics and specification provided in the ASMF, the Applicant is requested to unambiguously lay down the specification used by the Applicant to control quality of the drug substance [11]. This could as well include descriptions of own analytical methods, if relevant. The respective documents should be provided in a separate Module 3.2.S, under headings 3.2.S.4.x as appropriate.

In a CEP-backed MA dossier, the volume of information actually contained in Module 3.2.S is usually very small. Inherently, Certificates of Suitability are deemed to replace the data of the corresponding sections and therefore in principle no further additional information is necessary [14]. Only those sections of Module 3.2.S that provide information not covered by CEPs should be populated while the CEPs themselves are submitted under 3.2.R. As for ASMFs, the Applicant could be requested to submit an own drug substance specification under heading 3.2.S.4.1 accordingly.

Table 3 in Chapter 6.2.2 summarises the essential implications on Module 3.2.S structure applicable for most situations with Small Molecules.

5 Biotech Products

In this thesis, the term 'Biotech products' comprises Biologicals and ATMPs as described in Chapters 3.2.

5.1 Regulatory Aspects in the EU

5.1.1 Biologicals

As already marked in Chapter 3.2.1, biological drug substances are far more complex than Small Molecules. Due to the complex manufacturing and the fact that the substance's quality is determined by the process itself, rarely more than one drug substance manufacturer is present in the MA dossier.

Biologicals are far away from being "well-defined", hence both use of the ASMF and the CEP are not allowed with them. Consequently, always the entire drug substance documentation must be included in Module 3.2.S.

For an MAA for Biologicals, the CP is obligatory because they fall under the mandatory scope as detailed in Regulation (EC) 726/2004 [9]. This is applicable to new Biologicals as well as to so-called Biosimilars, i.e. "generics" of established Biologicals.

5.1.2 Advanced Therapy Medicinal Products (ATMPs)

ATMPs are even more sophisticated products than Biologicals. ATMPs range from nucleic acid-carrying virus particles over living cells to complete engineered tissues.

Most gene therapy products could be, highly simplified, considered as combination of a number of virus proteins in which nucleic acid coding for the desired polypeptide is incorporated. In other words, they are a combination of several Biologicals (polypeptides) with a nucleic acid component. Hence, in principle, requirements on quality documentation for Biologicals also apply for gene therapy products.

In contrast, somatic cell therapy products and tissue-engineered products consist of living cells, which means they contain a huge number of "substances" forming cellular components or even inter-cellular materials (tissues). Even the smallest unit of these products, i.e. single cells, dramatically exceed the dimensions of a virus particle. Therefore, on top of principle requirements on quality documentation for Biologicals, extended information on product quality must be provided for these ATMPs. Unambiguous description, reproducible manufacturing, and precise specifications of ATMP products are a big challenge, too.

For most ATMPs, biotechnological and clinical product development are inextricably linked to each other. Therefore, having more than one manufacturer is practically impossible.

Like Biologicals, ATMPs are in the mandatory scope for the CP at the EMA, where they will be assessed by a dedicated Committee, the CAT (Committee for Advanced Therapies) [8].

5.2 Implications for the Granularity of Module 3.2.S

Quality determination of Biotech products involves a combination of physico-chemical-biological testing, together with the production process and its control. Even though the concept of Biosimilars [7] has been developed and these substances are not considered to be NAS, in fact substance produced at different sites by different processes will never be identical. Module 3.2.S for Biotech products will therefore never include an abridged data package. The requirements described for NCEs (Chapter 4.2.1) are fully applicable for Biotech products as well.

However, due to their complexity, a number of additional data must be acquired compared to Small Molecules [13]. The focus is again on identification, manufacture & development, and control of the drug substance, just as for NCEs.

(1) Identification: Drug substances of Biotech products are large molecules, or, in case of ATMPs, even cellular components. Hence, information beyond a structural formula is needed to describe them sufficiently. For proteins, this includes for example the amino acid sequence, sites of disulphide bonds or glycosylation, and information on secondary and higher-order structures. In addition, data on biological activity, purity, or immunochemical properties could be presented.

For ATMPs, identity encompasses even higher structures, like virus particles with defined nucleic acid for gene-therapy products. For cell-based and tissue-engineered products, properties of characteristic cellular and non-cellular components up to histological level must be defined and described. In addition, biochemical, metabolic or immunological action should be characterised.

eCTD headings for presentation of the information are primarily 3.2.S.1.2, 3.2.S.1.3, and 3.2.S.3.1, but also 3.2.S.3.2 for data on impurities or 3.2.S.5 for definition of reference standards.

(2a) Manufacture: Because the manufacturing process determines the quality of Biotech products, the requirements on its documentation are extensive.

Starting materials

For biotechnological processes, a huge number of materials are needed, including, e.g., components of buffers and media, for which data must be provided. Furthermore, substantial information on source, generation, and analysis of gene-modified cells as well as data on the derived cell banks are requested. Finally yet importantly, a number of substances used in the process

are of biological origin like Albumin, FCS, or enzymes, which require further detailed documentation e.g. on their quality and virus safety.

For cell- or tissue-based ATMPs, source material are usually donor cells or tissues [15], for which definitions of selection criteria and material specification have to be set up. As sterilisation is not feasible for these materials, minimising the risk of transmitting diseases must be addressed.

According documentation must be included primarily under heading 3.2.S.2.3 for control of materials and 3.2.A.2 for biological safety aspects.

Manufacturing process description and validation

Biotech manufacturing processes typically include critical steps of cell culture, harvest, purification, and potential subsequent modification steps. Exact conditions, incubation or processing times, critical testing points and parameters must be determined and explained. For most test methods, validation data is required. Finally, validation and thus reproducibility of the entire manufacturing process must be demonstrated. Another important aspect is the definition of production scale and batches.

Usually even before start of the actual manufacturing process for cell- or tissue-based ATMP, donor cells or tissues have to be sourced. The parameters for selection of appropriate material and the procurement procedure must be explained. The actual manufacturing process will already begin with the procedure of obtaining and isolating the desired cells or tissue from the donor material. Next steps include cell manipulation or tissue engineering and further processing. Particular focus should be put on containers, which are used during transport or storage, and their compatibility with the product. The requirements for Biologicals as outlined above apply to manufacturing of ATMPs accordingly.

Documentation relating to manufacturing process should be primarily submitted under eCTD headings 3.2.S.2.2, 3.2.S.2.4, and 3.2.S.2.5.

(2b) Development: The development of the complex manufacturing like for Biotech products is a long lasting process. In most cases, optimisation of the manufacturing process is ongoing still during conduct of non-clinical and clinical studies. That means that the product manufactured for these studies will not be identical to the product from the final process as described in the MA dossier.

Therefore, the developmental history of the manufacturing process should be provided in the MAA dossier. This should for example, include changes to the process itself or to critical equipment, and assessment of the significance of impact to substance quality. Historic batches and if they were used in the studies should be explained. Comparability information should be provided for batches produced before and after significant changes. However,

comparability assessment may not only be restricted to analytical testing, but could also involve non-clinical and clinical studies.

Most information on development and comparability should be placed under heading 3.2.S.2.6; data on method description or justification of critical steps and specification limits may be better located in heading 3.2.S.2.4. If relevant, additional information on sites and manufacturing equipment should be submitted in 3.2.A.1.

Lastly, if nonclinical or clinical studies were involved, the study reports will be located in Module 4 or 5, respectively. Discussion of study results should be done in the respective Module 2 documents.

(3) Control of drug substance: As quality of Biotech products is determined by both physico-chemical-biological testing and its production process and controls, a number of most often non-standard analytical procedures are needed. These methods must be developed and established. Accordingly, a considerable number of documents on description, development, and validation of analytical methods are required in the MA dossier.

Affected eCTD headings are primarily 3.2.S.4.2 and 3.2.S.4.3. However, development of manufacturing process and of associated controls are closely related. If methods are not relevant for product release, therefore, data for these methods might also be placed under 3.2.S.2.4 or 3.2.S.2.6.

Submission of a Control Strategy Summary document could be good way to make the reviewers understand the development concept (see Chapter 5.3).

5.2.1 Remarks for ATMPs

Especially for cell- or tissue-based ATMPs, precise definition of raw material vs. drug substance vs. drug product (or even vs. drug product ready for application) can be very difficult. Nevertheless, on these definitions depend further cut-offs like start and end of manufacturing processes or distinguishing between IPC and Release tests. If definitions should change during the MAA assessment, this might also affect location of related reports.

ATMPs are very special and often extremely expensive medicinal products, which despite all development work, in general bear high risk potential. Therefore, such products are developed for (ideally cure of) severe diseases for which no other treatment option currently exist, often for orphan indications. Generally, for treatment of the indicated disease and use of the ATMPs only few specialised users in the EU or worldwide exist. They have in-depth expertise with the disease and some of them are usually already involved during the (clinical) development of the ATMP. The expertise of these specialised users is important, because in some cases the user has to perform additional steps for making the ATMP ready for use, which might fall under the definition of "manufacture". Examples are reconstitution e.g. thawing and re-suspending the product with subsequent testing steps like cell count or viability

assessment. For these steps, documentation on performance, specification and their justification must be provided in the MA dossier as well.

5.2.2 Remark for Biosimilars

In analogy to generic products, the concept of Biosimilars bases on the similarity with approved Biologicals with known clinical profile. This similarity should be demonstrated with the so-called biosimilar comparability exercise. This exercise usually includes physicochemical and biological characterisation as wells as nonclinical and clinical studies [16]. A large amount of data from that exercise will be related to drug substance similarity, demonstrated by analytical assessment. In contrast to other development or analytics documentation, these data should usually be placed in section 3.2.R [17].

5.3 Brief Excursus to Control Strategy

As can be derived from Chapters 4.2.1 and 5.2, manufacturing process development of a new drug substance is a continuous and multifaceted process. Understanding of the substance evolves with increase of data being gathered on identification, manufacture, and suitable controls. None of these aspects can be thoroughly addressed without looking at the others. Having in mind this close interdependence, a common development of all aspects could facilitate development.

In ICH Guideline Q11 [18], integral approaches on developing and understanding the manufacturing process of the drug substance are described. Process development inherently includes definition of a strategy to control the process and the quality of the final substance. The guideline defines a control strategy as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality." Control strategy should cover all relevant stages of the process and products, like control of raw materials, design of the manufacturing process, IPC, or release testing of the final product.

In the MA dossier, data related to establishing manufacturing process, specifications, and analytical methods are submitted in the respective sections of the dossier. However, this information will be widely spread over the dossier, sometimes making it difficult to the reviewer to understand the overall strategy.

ICH Guideline Q11 therefore introduces the idea to submit a Control Strategy Summary "in either a tabular format or in a diagrammatic format, to aid visualisation and understanding. Ideally, the summary should explain how the individual elements of the control strategy work together to assure drug substance quality." [18] This summary should refer to those documents in the dossier that contain the detailed information. The Guideline proposes to place the summary document under heading 3.2.S.4.5 Justification for Specifications, which indeed might be the most suitable location.

6 Dossier Planning and Strategic Considerations

6.1 Brief General Aspects of Dossier Planning

Dossier planning should take into account a number of aspects. Most important, the MAA dossier must support the goal of getting approval for the medicinal product after assessment by the Competent Authority (CA). This requires easy accessibility of information throughout the dossier for the CA. Important aspects are consistent presentation as well as clear and logical arrangement of documents. In addition, adequate use of bookmarks and hyperlinks should facilitate navigation through the dossier and single documents, and improve general good handling.

The dossier will not remain constant after MAA submission. Throughout the lifetime of the MA, the dossier will undergo changes resulting from post-approval procedures. These changes will be implemented in the dossier by addition of new documents or modification or deletion of previously submitted ones. In the eCTD specification, the corresponding lifecycle operation NEW, REPLACE, and DELETE are defined.

Finally, dossier planning should consider planned or expected changes early on, too.

6.2 Granularity of Module 3.2.S

Dossier planning considerations are of course not restricted to Module 3.2.S; however, they will be discussed only for this part of the CTD in this thesis.

In eCTD, Module(s) 3.2.S will be identified by values of the attributes for Drug Substance Name and Manufacturer (see Chapter 2.3). In essence, the decision for a certain granularity approach will be reflected in the values of these attributes, and vice versa. As these attributes cannot be altered during lifecycle, their values should be chosen very carefully. The manufacturer attribute for examples does not need to match exactly the companies ('ABC Werke GmbH & Co. KG, Bitterfeld') but should just identify the manufacturer unambiguously ('ABC'). That way, it will remain correct also after potential changes to the manufacturer's address or minor changes to the name or legal form. Similarly, the Drug Substance attribute should be generic, ideally the INN.

In line with (e)CTD Guidelines, it is not mandatory to populate each section in any Module 3.2.S. Therefore, even if there is just one document specific for one manufacturer, a separate Module 3.2.S could be created.

The Granularity Document allows for one or multiple documents to be placed at the lowest hierarchical level in Module 3.2.S (see Chapter 2.4). Thus, in principle the Applicant has the option either to combine all data into one document under the respective heading or to use single documents for every piece of information. For multiple document approaches, meaningful leaf titles could be used for further differentiation, for example for method validation reports in 3.2.S.4.3 ('Validation Report – C18 RP-HPLC' instead of

'32s43-6'). The choice of the best approach should depend on overall volume of information for each heading in the MA dossier and lifecycle considerations.

Fundamentally, dossier planning for the drug substance part could be reduced to a decision on number of Module(s) 3.2.S and, derived from that, the granularity of each Module. Some strategic consideration will be helpful to find the best overall granularity. A selection will be discussed in the following chapters with general consideration on lifecycle issues and specifics for Small Molecules or Biotech products. In Appendix 13.2 a simple decision tree is depicted, which outlines a basic approach to start granularity planning.

Lastly, it should be kept in mind that the eCTD is an international standard; hence, a dossier created for an MAA submission in the EU can potentially be re-used in other regions. If submissions are planned for the same product in further regions, their requirements on documentation and granularity should be considered as well before making a final decision. However, as this thesis focusses on the situation in the EU, this aspect will not be discussed further.

6.2.1 Strategic Considerations Related to Lifecycle

Changes to the content of the eCTD can only be made on document level (see Chapter 2.3). This can be done by either adding NEW documents or exchanging existing one. For updates, however, even if only little of a documents' content is revised, the entire document has to be REPLACEd. That means that both the new and the previous content will appear as updated information to the reviewer. Therefore, to avoid future misunderstandings, dossier planning should consider which contents will likely be subject to changes and which will persist for longer time.

A good estimation of change-susceptibility for certain sections can be derived from the Variation Regulation [19], where information is given on classification of changes and required documentation to support it. For variations to the drug substance documentation, which are addressed in chapter B.I, changes relating to manufacture, control, stability, and the container closure system are listed. Appendix 13.1 provides an overview on most common matters of variations, which might act as basis for starting lifecycle considerations for dossier planning.

At first approximation, for change-susceptible sections, a multiple document approach appears to be the best option and analogously just a single document for persistent sections. However, some sections are usually small anyway, thus a multiple document approach does not make sense even in case of frequent changes. On the other hand, presumably persistent sections may contain a lot of information for which use of multiple documents may enhance reviewability though. A decision on can only be made on basis of the specific situation.

6.2.2 Small Molecules

Approaches for Dossier Planning

For MA dossiers with Small Molecule drug substances, the granularity of (each) Module 3.2.S is quite straightforward in most cases. Typical situations will be discussed in the following.

For NCEs, usually only one manufacturer exists at the time of MAA submission, therefore having just one Module 3.2.S is appropriate. The Applicant had typically been widely involved in development of the substance and therefore has deep knowledge about all aspects of the substance. In the MA dossier, the entire documentation should be provided in a single Module 3.2.S. Nevertheless, for NCEs exists the possibility to make use of an ASMF, too.

When using ASMFs, the AP provided by the ASMF holder should be placed in Module 3.2.S without changes [11]. With multiple ASMFs, each AP should form a separate Module 3.2.S. Potentially required additional information from the Applicant should be submitted in a separate Module 3.2.S.

For CEP-backed drug substance documentation, potentially required additional information (which should only be very limited) should be combined into one Module 3.2.S, even in case more than one CEP is used.

Decision Finding

As a first step, the Applicant should look at the number of drug substances. Information relating to more than one drug substance must not be submitted in a single Module 3.2.S; but at least one Module 3.2.S per drug substance is needed (if not exempted totally by use of a CEP).

Secondly, the number of manufacturers per drug substance should be assessed. In most cases, a separate Module 3.2.S for each manufacturer should be appropriate to ensure flexibility to manage manufacturer-specific lifecycle. However, if information from all manufacturers is very similar, a combined Module 3.2.S is possible as well. Those few documents that are manufacturer specific should be identified by leaf titles then.

For well-known substances for which a number of potential drug substance suppliers are available, post-approval changes in the manufacturer are quite common. For example, if the original manufacturer had a rather small production scale that was sufficient for clinical study supply, could be too less for expected sales volume after approval. Such changes can have deep impact on the overall structure and granularity of Module 3.2.S. Organising Module(s) 3.2.S in a way to be able to easily add data from the new manufacturer and/or delete it from the previous one, will prevent lifecycle and reviewability problems later on.

As a general recommendation, creation of separate Modules 3.2.S for each manufacturer is the most straightforward way of handling data from multiple suppliers and keeping maximum flexibility for most lifecycle changes. For well-

characterised substances with established manufacturing and analytics, the approach of submitting documents that are applicable to all manufacturers under a common Module 3.2.S could be workable. However, in case of addition or deletion of manufacturers it might result in inconsistencies or the need of building a new separate Module 3.2.S for the new manufacturer.

Depending on whether it is an NCE or a well-known substance and whether ASMF or CEP are used, the amount of data in Module 3.2.S can vary considerably (see Chapter 4.2). For sections with a lot of content, the question must be answered, whether a multiple document approach made sense (see Chapter 6.2.3 for NCEs).

Table 3 summarises the essential implications on Module 3.2.S structure applicable for most situations with Small Molecules in the EU and should be read in conjunction with the decision tree in Appendix 13.2.

Table 3: Organisation of Module 3.2.S for Small Molecules

For all situations:
Never submit data for multiple drug substances in one Module 3.2.S

	NCE or no ASMF/CEP	**ASMF**	**CEP**
How many Modules 3.2.S? [attribute value]	1 for each manufacturer [Manufacturer]	1 for each AP [ASMF holder]	Commonly one combined Module 3.2.S for additional info to the CEPs or own controls etc. [Common/All]
Additional Modules 3.2.S for Applicant's specification [attribute value]	Not needed	Usually requested [Manufacturer] or [All]; to keep most flexibility	

Module 3.2.S Granularity

Where are extensive data or reports expected?
Could more than 1 document make sense?

	NCE	**ASMF or non-NCE**	**CEP**
Identification & Characterisation	Yes S.3.1, S.3.2, S.5	Unlikely (S.3.2)	No
Development & Manufacture	Yes S.2.3, S.2.4, S.2.5, S.2.6	No	No
Control of drug substance	Yes S.4.2, S.4.3, S.4.5	Likely S.4.2, S.4.3, S.4.5	Common S.4.2, S.4.3, S.4.5

6.2.3 New Active Substances and Biotech Products

Approaches for Dossier Planning

Much of the data required for the MAA submission for NAS, for example on identification or development, will not be changed throughout the lifetime of the product dossier; normally these data are provided as reports. However, other contents of the dossier that refer to or summarise these reports could be subject of variations. As eCTD changes can only be submitted at document level, it is recommended to have reports and summarising documents separated. Clearly naming the matter of the report documents in the leaf title will enhance reviewability.

For Biotech products, the introduction of a new drug substance manufacturer is unlikely; nevertheless, substantial variations to the manufacturing are not uncommon. Such changes could result in final drug substance quality, which is not exactly identical to the batches manufactured by the initially approved process. An example is the upscaling of production. Even if performed at the same site, larger scales usually require different equipment, which could potentially result in quality deviations. For instance, results of cell cultivation steps might be different due to unforeseen differences in growth conditions. Therefore, such variation applications require documentation on process development and thorough validation of the new manufacturing process including all relevant IPCs as well as stability data for new batches.

Another typical example could be a change in quality or supplier of critical raw material, e.g. growth factors for cell cultivation process or enzymes for purification steps. As such raw materials themselves are products made by biotechnological processes, they might differ from the previous material in their final quality like, e.g., the glycosylation pattern. This could have an impact on biological activity, which in turn might influence cell cultivation.

Handling such changes and their extensive documentation requirements in the existing Module 3.2.S can get difficult with high potential for inconsistencies. Therefore, instead of replacing the existing documents, addition of the documents as NEW, differentiated by the leaf title could be appropriate. Alternatively, the option of creating a separate Module 3.2.S for substance from the new process can be considered. Differentiation would be realised by the drug substance attribute and leaf title, ideally. Upon approval of the variation, deletion of summarising documents from the outdated process can be made with a consolidation sequence.

Decision Finding

Documentation related to NCEs or Biotech products is enormous and complex. Therefore, dossier planning should focus on making this data reviewable and getting the reviewer to understand the product. Consistent terminology in the leaf titles and throughout the documentation and sufficient granularity under critical headings will facilitate this process.

7 Analysis – Suitability of the Granularity Document

In this Chapter, an analysis is performed with view to the Granularity Document in its current version, M4(R3) [2]. Impacts of the proposed revisions for new version M4(R4) [20] will be discussed in Chapter 8.

The objective of the ICH Guideline M4 is the provision of "a well-structured Common Technical Document for applications that will be submitted to regulatory authorities", i.e. being a format applicable as a standard for MA dossiers for any type of drug substances.

As described in Chapter 2.4, the Granularity Document requests for Module 3.2.S that documents must be submitted under the lowest defined heading only, but one or multiple documents can be provided under each heading. The appropriateness of this granularity for presentation of data in MA dossiers for different types of drug substances will be analysed in the following.

7.1 New Chemical Entities

For NCEs, the entire documentation must be provided in the MA dossier, originating either directly from the Applicant or from an ASMF (see Chapter 4.2.1). For either option, the Granularity Document's demands appear well suited. The required documentation contains enough information to justify at least one document under every heading, except for 3.2.S.1.x. For sections where more data must be submitted, the multi-document option is useful (see Chapter 6.2.2). For the lifecycle of NCE dossiers, if properly planned, the granularity should still fit well; at least as long as the substance does not become candidate for a CEP (see below).

7.2 Well-known Small Molecules

For these substances, volume of data to be submitted by the Applicant is normally rather small. Particularly for sections whose content is very unlikely to change, it could be easier to combine contents from lowest level into one document at a higher level, e.g. for section 3.2.S.1. Similarly, section 3.2.S.3 is imaginable for roll-up; however, impurity profile could change due to future development of more sophisticated analytical methods (see Chapter 6.2.2).

When using a CEP supplemented by minimal common data from the Applicant for, e.g., specification, it could be desirable to combine that small set of data into one document already at 3.2.S level. This approach is even thinkable if using an ASMF for these substances, because the ASMF's content will be assessed in the ASMF dossier itself, but not in the MA dossier. In addition, an ASMF is likely to be referenced by a number of MA dossiers, thus the CA is already used to the content of the current ASMF version. Consequently, providing the entire ASMF in just one document could suffice.

7.3 Biotech Products

The enormous amount of data supplied with MA dossiers for Biotech products must make use of the multiple document approach for many sections (see Chapter 5.2). While this approach is fine for most sections like 3.2.S.1.x or 3.2.S.4.x, a still deeper granularity can be imagined under headings 3.2.S.2.3, 3.2.S.2.6, or 3.2.S.7.3, for example.

Section 3.2.S.2.3 concerns Control of Materials; optional subsections distinguished by material are thinkable, comparable to section 3.2.P.4 (see Chapter 8). As for excipients, suppliers or quality of raw materials can change, what may have significant impact on the substance quality (see Chapter 6.2.3). By having raw material documentation structured similar to section 3.2.P.4, a better tracking and reviewability of this information could be achieved. Stability data in section 3.2.S.7.x could be structured accordingly. Similar consideration can be made for sections 3.2.S.2.5 and 3.2.S.2.6, concerning both process development and validation. For changes to the manufacturing process, again with possibly significant impact on overall quality, differentiation by process version can be imagined.

Admittedly, a comparable degree of differentiation could already be achieved by consequent leaf title naming and/or use of node extensions. Nevertheless, such approaches need to be planned well in advance and thoroughly implemented with the initial MAA submission to have consistent structure with later lifecycle changes. Although node extensions are feasible and permitted in the EU, such structures always bear the risk of lifecycle problems if not understood and maintained properly. A built-in option with the Granularity Document and the eCTD specification allowing optional attributes in these sections could facilitate consistent structures from the very beginning of dossier compilation. Nevertheless, rolling-up of neither node extensions nor attribute-distinguished sections in later lifecycle would be possible without complete rebuilding the sections.

A further aid of providing complex development data in a better reviewable form could be the use of a Control Strategy Summary (see Chapter 5.3). If included, ICH Guideline Q11 proposes locating this summary under heading 3.2.S.4.5. But control strategy also includes specification and method development, therefore placing the summary at 3.2.S.4 level could be the better option.

Furthermore, control strategy ranges to aspects of manufacturing process development or identification of drug substance and related substance as well. Hence, an option to place a summary document under e.g. heading 3.2.S.2 or 3.2.S.3 could be desirable as well.

7.4 Summary

As the Granularity Document permits placing multiple documents into under any heading of the eCTD, in principle all types of drug substances can be handled. The proposed granularity fits well to substances whose documentation suffices to fill into all sections while not overcrowding any one. For well-known substances with only few data, granularity can become inappropriately scattered, while on the other hand for complex substances more sub-granularity could be desirable. If submitted, a top-level location of control strategy summary document would be favoured.

A brief summary on analysis results is shown in Table 4, where it is indicated which improvements would be desirable for different drug substance types.

Table 4: Assessment of Suitability of the Granularity Document

<table>
<tr><th>Section</th><th>NCE</th><th>Well-known Small Molecule</th><th>Well-known CEP/ ASMF</th><th>Biotech products</th></tr>
<tr><td>3.2.S.1</td><td>roll-up to S.1</td><td>roll-up to S.1</td><td rowspan="8">Option to roll-up to higher levels or even to 3.2.S</td><td>Suitable</td></tr>
<tr><td>3.2.S.2</td><td rowspan="7">Overall suitable</td><td>Suitable</td><td>Sub-granularity for e.g. S.2.3, S.2.5, S.2.6, (S.2.4)</td></tr>
<tr><td>3.2.S.3</td><td>roll-up to S.3</td><td>Sub-granularity for S.3.2 Impurity analysis</td></tr>
<tr><td>3.2.S.4</td><td>Suitable</td><td>Sub-granularity for S.4.2, S.4.3</td></tr>
<tr><td>3.2.S.5</td><td>Suitable</td><td>Overall suitable</td></tr>
<tr><td>3.2.S.6</td><td>Suitable</td><td>Overall suitable</td></tr>
<tr><td>3.2.S.7</td><td>roll-up to S.7</td><td>Sub-granularity for S.7.1, S.7.3</td></tr>
</table>

8 Revision of the Granularity Document

The Granularity Document in its current version has been approved in January 2004. Essentially, the currently valid version of this document has not been changed for more than 12 years. During this period, the CTD format and later the eCTD indisputably became the standard for data submission of regulatory information for human medicines. In the meantime, hundreds of new guidance documents for drug development have been published and requirements on data to support an MA application have been further specified.

Time had come for a critical review of the Granularity Document whether its recommendations were still adequate nowadays. In parallel, the eCTD standard has been further developed, with eCTD version 4.0 coming closer to implementation (see Chapter 10). Implications from this Next Major Version on the Granularity Documents required estimation as well. Recently, the revision process is advancing to finalisation at ICH [21]. Based on the probably final version [20], an analysis for Module 3.2.S is performed, investigating if and how findings from Chapter 7 have been addressed.

8.1 Changes to Module 3.2.S Granularity for eCTD v3.2.2

The implemented revisions of granularity requirements for submissions following the current eCTD v3.2.2 specification are of only limited extent. Generally, there are no changes for Module 3.2.S granularity, with the exception that an optional Control Strategy Summary document now may be located directly under heading 3.2.S.4; however, a dedicated filename for this document is not provided. Overall, the potential for improvement as analysed in Chapter 7 has not been used.

Albeit acknowledging that the designated successor is only few steps away, eCTD v3.2.2 is still the standard for new MAA submissions. It is understood that, in the light of advancing v4.0, would not be worth the effort to establish a new minor version supporting new attributes that would be beneficial for complex Biotech products. Still, at one point, revisions that are more courageous were expectable: The opportunity has not been taken to simplify submission of drug substance data for well-known substances by rolling-up the Module 3.2.S to one or few documents at higher hierarchical levels.

However, at another location of the eCTD, a significant change is made relating to the drug substance documentation. Until Revision 3, the Applicant had the choice either to submit Module 2.3 Quality Overall Summary documents under headings 2.3.S.x or one level higher. With Revision 4, only the high-level approach is accepted. This change could a disadvantage for NCEs or Biotech products; for well-known Small Molecules, however, this is not an improvement at all, because this option has already existed before.

Changes for section 3.2.P.4 are summarised in Chapter 9.6.

9 Excursus to 3.2.P.4 Drug Product – Excipients

9.1 Introduction

Excipients are contained in almost every medicinal product. In the CHMP Excipients Guideline EMEA/CHMP/QWP/396951/2006 [22], they are defined as

> *the constituents of a pharmaceutical form apart from the active substance.*
>
> *Excipients include e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances etc., as well as the constituents of the outer covering of the medicinal products, e.g. gelatine capsules. [..] Information on the excipients used in a medicinal product should be provided in part 3.2.P.1, 3.2.P.2, 3.2.P.4, and 3.2.A.3 of the dossier.*

As stated above, information on excipients are an integral part of the quality documentation to be submitted in eCTD Module 3 in the relevant sections. While 3.2.P.1 and 3.2.P.2 contain general information on the qualitative and quantitative composition of the medicinal product, the actual information relating to the excipients should be included in section(s) 3.2.P.4 and, for novel excipients, in 3.2.A.3. In the eCTD v3.2.2 specification, both sections are repeatable and an optional "excipients" attribute exists for them, which allows for a more detailed structure.

There are 6 sub-headings defined for section 3.2.P.4, under which, according to the current Granularity Document M4(R3), excipients' information should be placed in the MA dossier, as shown in Table 5.

Table 5: Granularity of Section 3.2.P4 [2]

3.2.P Drug Product	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
Key		
Documents rolled up to this level are not considered appropriate		
One or multiple documents can be submitted at this level		

Expected documents and contents in section 3.2.P.4 for excipients of different regulatory status are briefly summarised in the following.

9.2 Compendial Excipients

A considerable number of excipients have a long history of use in medicinal products. The majority of the most common excipients is already monographed in pharmacopoeias. Thus, the potential risks of these substances are well known, requiring less documentation. In fact, reference to the monograph or submitting a CEP would be sufficient [22]. This information can be summarised in a common document for all compendial excipients, which is also unlikely to undergo changes during lifecycle, except for supplier changes.

9.3 Non-compendial Excipients

Although not monographed, significant experience exists with the use of many non-compendial excipients in medicinal products, limiting the amount of required data. However, a simple reference to a pharmacopoeial monograph is not possible, thus still details regarding the specification and analytic procedures must be provided, for which a separate document under each specified heading might be appropriate [22]. Nevertheless, the content is unlikely to change in future, at least as long as the excipient does not become compendial. There is no ASMF-like approach established in the EU.

9.4 Excipients of Human or Animal Origin and Novel Excipients

Albeit not obvious from the eCTD v3.2.2 specification, under headings 3.2.P.4.5 and 3.2.P.4.6 general information on use and nature of excipients of human or animal origin and novel excipients should be submitted. These documents should not be physically placed under an excipient-specific subfolder, but at 3.2.P.4 level; nevertheless, an excipients attribute should be used for these documents in the xml file.

Excipients of human or animal origin potentially bear the risk of transmitting adventitious agents. Therefore, information on, e.g., sources, specifications, risk minimisation measures etc. should be provided. Section 3.2.P.4.5 should only be used for a brief summary, while details on the matter should be provided in section 3.2.A.2.

Novel excipients i.e. "excipients used for the first time in a drug product or by a new route of administration" [22] require a considerably larger volume of documentation to demonstrate their safety. According to the ICH Guideline M4Q(R1) [3], "full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical)" should be provided. These requirements are in principle comparable to those for the active substance itself. Section 3.2.P.4.6 should only be used for a brief summary. For submission of the detailed information, an individually granulated section 3.2.A.3 is to be used for each novel excipient. However, the exact structure for organisation of documents in 3.2.A.3 is not clearly defined in the CTD guidance, but it could be in principle oriented on Module 3.2.S structure.

9.5 Implications for Dossier Structure, Attributes, and Lifecycle

It was the original intent of the CTD to establish a common structure applicable to the presentation of data for any excipient. However, excipients are a heterogeneous group of substances ranging from simple H_2O to complex structures like polypeptides. As outlined above, requirements for information on the excipients significantly differ with the regulatory status of the excipient.

Due to this heterogeneity, soon discussions up to ICH level started about the best approach for handling content in section 3.2.P.4 in eCTD v3.2.2. The main topics concern the general granularity at the time of MAA dossier compilation and the lifecycle management of documents with focus on status changes of excipients. In the Q&A document [23], regularly updated on the website, the ICH eCTD IWG published practical recommendations on the use and structure of this section (Q72 – Q75); occasionally even contradicting the Granularity Document.

For initial submissions, in general three options are identified (Q73):

- Option 1: Using a single document covering all 3.2.P.4.x headings for all excipients; the attribute could be a general term like "all". Inconsistent with the Granularity Document, the document should be placed at 3.2.P.4 level.

- Option 2: Using one separate document for each excipient covering all 3.2.P.4.x headings, distinguished by the excipient attribute. Again, documents should be placed at 3.2.P.4 level, being inconsistent with the Granularity Document. A section 3.2.P.4 does not have to be limited to exactly one excipient but could also be used for a group of excipients, for example all compendial excipients.

- Option 3 is the literal approach, i.e. the creation of a separate 3.2.P.4 section with P.4.x granularity for each excipient, distinguished by excipient attribute.

A combination of Options 2 and 3 is possible. For a single document under heading 3.2.P.4, the filename "excipients-*var*.pdf is suggested. Despite not being explicitly defined in eCTD v.3.2.2 specification, this filename can be considered acceptable.

These different approaches should allow for more flexibility in defining a suitable granularity for the individual case of the product. Option 1 is most attractive for products with only compendial excipients, which require very small information. Option 2 offers more flexibility for products containing excipients with different volume of documentation, where 3.2.P.4 sections suited individually to the respective excipient can be created. Excipients can also be grouped, e.g. content for all compendial excipients can be managed in a common heading 3.2.P.4, while the documents for the non-compendial excipients are placed in separate 3.2.P.4 sections.

Option 3 is always a correct way of presentation, however, a large number of documents with only very small content are not very reviewer-friendly and will need more attention during lifecycle maintenance. Consequently, the Q&A recommends avoiding this approach for products containing many compendial excipients.

When planning the dossier also future lifecycle should be considered. Contents for compendial excipients and most non-compendial excipients are unlikely to undergo frequent and significant changes. Therefore, deep granularity does not add benefit because no high flexibility for future lifecycle is needed. In addition, changes to the dossier can only be made by replacing one document with another, therefore a later rolling up of split contents into one document, i.e. transitioning from Option 3 to Option 1 or 2, is not trivial. Furthermore, attributes cannot be changed in eCTD v.3.2.2 and thus need to be planned well ahead to be flexible e.g. in case an excipients is renamed. Use of more general terms is recommended generally, e.g. "coating agent" instead of "Eudragit xyz".

Ultimately, an excipient's regulatory status is not static; novel excipients might lose the status of novelty or occasionally could become compendial over time, as might also be the case for hitherto non-compendial excipients. Such changes would significantly reduce the amount of documentation needed for the respective excipient. The question how to manage lifecycle in this case is the second big excipients topic in the Q&A Document [23], discussed in Q75.

Three general cases are identified and described:

- Excipient is renamed: Attribute re-naming is not possible. If the Applicant desires to have the new name in the attribute, the old leafs must be DELETEd and the documents submitted as NEW under the new attribute.
- Novel excipient is no longer novel: The excipient should already have its dedicated section in 3.2.P.4, updating the documents there is straightforward; no need to change the attribute. Documents in 3.2.A.3 relating to information on control of the excipient should be kept.
- Non-compendial excipient becomes compendial: Although there are some other constellations, the basic question is how to incorporate documents from a stand-alone section 3.2.P.4 into a common "compendial" 3.2.P.4. Recommendation is to REPLACE the documents in the "compendial" 3.2.P.4 section incorporating information on the newly compendial excipient and DELETE all documents from the excipient specific 3.2.P.4.

The recommended solutions are quite straightforward. However, DELETing documents and adding them with identical content as NEW in some other section can result in a very confusing current view in the eCTD viewing tool and the lifecycle of documents appears interrupted.

With eCTD v4.0 coming closer, it could be an option to just wait and revise section 3.2.P.4 later using the improved lifecycle opportunities from eCTD v4.0 (see Chapter 10).

9.6 Analysis – Suitability of the Granularity Document

Granularity for section 3.2.P.4 as outlined in the current version of the Granularity Document (R3) only fits to the need of data requirements for non-compendial, non-novel excipients. For these, information regarding the control is sufficient and can be appropriately placed under 3.2.P.4.x headings.

For compendial excipients requiring very small information, distribution of that content over multiple documents is not useful. This has been acknowledged by the ICH; in the Q&As Q75, they confirm that information can be summarised into one document at 3.2.P.4 level, although this is inconsistent with the eCTD specification and the Granularity Document.

Revision of the Granularity Document

In the recent revision of the Granularity Document (see Chapter 8), ICH now formally addresses the apparent inconsistencies. The option of submitting documents directly under this 3.2.P.4 heading has been implemented. However, eCTD v3.2.2 specification still does not explicitly include an excipients-*var*.pdf what will result in violation of a best-practice validation criterion.

The known lifecycle issues have not been solved either. Admittedly, this would have need a revision of eCTD v3.2.2 specification, what might be unreasonable as discussed in Chapter 8.1).

The option to wait until implementation of eCTD v4.0 might become realistic. The changes to section 3.2.P.4 coming along with eCTD v4.0 are briefly summarised in Chapter 10.1.2.

10 eCTD v4.0 Specification

The eCTD in its current form has evolved from the idea of transforming the paper CTD into an electronic form; in essence, just the backbone xml was added to the loose collection of files and folders. Like the CTD, the eCTD v3.2.2 index.xml is constructed in in a top-down approach starting from module level to section to subsection and ultimately to document, e.g. m3->m32->m32s->m32sx->xxx.pdf. An advantage at the time of implementation was that the migration to eCTD format was relatively easy to understand what surely contributed to the success of the eCTD. However, over time some downsides were realised. A big disadvantage is the strict granularity and inflexibility for document lifecycle management (see e.g. Chapters 6.2 or 9.5).

This disadvantage is addressed with the new eCTD v4.0 specification [24]. It is based on the HL7 Version 3 Regulated Product Submission (RPS) Release 2 Normative, whose scope is the definition of "the message for exchanging information electronically between Regulators and Industry" [25]. The eCTD v4.0 specification has been published with the eCTD v4.0 Implementation Guide v1.1 in January 2016 after having passed Step 4 approval at the ICH.

There are a number of significant changes compared to eCTD v3.2.2, however, only a few are in the focus of this thesis. It is acknowledged that the implementation of these concepts and functionalities requires a completely different xml-"backbone"; however, explanations that were more detailed would go beyond the scope of this thesis. The improvements regarding eCTD granularity are mainly resulting from three of the new concepts of eCTD v4.0, as described in the Implementation Guide [24].

> ***Document reuse**: Once a document has been submitted, eCTD v4.0 will allow for this document to be reused in the same context in a different submission unit, submission or application, reused in a different context in the same submission unit or application, or reused in a different context in a different submission unit or application. This is accomplished by assigning each document with a unique ID that can be referenced anywhere in the Regulatory Authority's environment.*
>
> ***Context of Use life cycle**: The Context of Use concept allows for advanced life cycle management operations. A Context of Use may be replaced by one or more Context of Use elements and vice versa (i.e., many to one) through the context of use life cycle.*
>
> *eCTD v4.0 supports the existing "new", "replace", and "delete" eCTD v3.2.2 life cycle operators; however the support for the "append" operation has been removed from the eCTD v4.0 specification. eCTD v4.0 also introduces the ability to apply changes to keyword definition display name values (e.g., drug substance/product names, manufacturers, dosage forms, indication, excipient, group title, etc.) without resubmitting the physical files or the Contexts of Use element.*

***Function of document groups**: In eCTD v4.0, documents are referenced by a Context of Use, which specifies where they are to be inserted into the CTD/eCTD table of contents when presenting a reviewable structure.* [..] *In eCTD v4.0, the Context of Use code and Keyword code combination functions to create a group of documents.*

Though their naming is different, some terms used in eCTD v3.2.2 and v4.0 specifications are comparable as shown below, permitting a first attempt to evaluate the consequences on Module 3.2.S granularity for dossiers according to proposed eCTD 4.0 specifications.

Table 6: Comparison of Terms Used in eCTD v.3.2.2 and v4.0 Specifications

eCTD v4.0	**Equivalent in CTD/eCTD v3.2.2**
Document	Document i.e. (pdf) file in the submission
ContextOfUse (CV*)	CTD Heading / Level in eCTD specification
Keyword	eCTD attribute (CV)/ node extension
Document group	node-extension, STF (CV)

* Controlled Vocabulary

10.1 Granularity Document for eCTD v4.0 Submissions

The revised Granularity Document defines granularity for eCTD v4.0, too. For this purpose, the document has been amended with two dedicated tabular overviews on Modules 2 and 3, respectively, and further explanations for eCTD v4.0 specific topics in six Appendices. The granularity for Module 3.2.S and section 3.2.P.4 is shown in Table 7.

Table 7: Granularity of Module 3.2.S and Section 3.2.P.4 [20]

3.2	3.2.S Note 2	3.2.S.1 Note 4		**Key**
		3.2.S.2 Note 2	3.2.S.2.1	Documents rolled up to this level are not considered appropriate and no document is to be present at this level
			3.2.S.2.2	
			3.2.S.2.3	One or multiple documents can be submitted at this level
			3.2.S.2.4	
			3.2.S.2.5	One or multiple documents can be submitted at this level, but its content is not rolled up from lower levels
			3.2.S.2.6	
		3.2.S.3 Note 2	3.2.S.3.1	
			3.2.S.3.2	
		3.2.S.4 Note 2	3.2.S.4.1	
			3.2.S.4.2	
			3.2.S.4.3	
			3.2.S.4.4	
			3.2.S.4.5	
		3.2.S.5		
		3.2.S.6		
		3.2.S.7 Note 2	3.2.S.7.1	
			3.2.S.7.2	
			3.2.S.7.3 Note 5	
	3.2.P Note 2	3.2.P.4 Note 8	3.2.P.4.1	
			3.2.P.4.2	
			3.2.P.4.3	
			3.2.P.4.4	
			3.2.P.4.5	
			3.2.P.4.6	

Note 2: Document(s) may be present at this level in addition to having document(s) at lower level(s); refer to Appendix B.

Note 4: The lower level of each heading included in CTD-Q at this point is unlikely to contain individual documents or files.

Note 5: For stability, the information may be provided in its entirety or per manufacturer, stability study protocol, and/or any other distinguishing information. Refer to Appendix C.

Note 8: For excipient guidance on when to use the 3.2.P.4 and/or 3.2.P.4.x level, refer to Appendix D.

Obviously new is the "blue" granularity. eCTD v4.0 provides the option of submitting documents at a higher level, if useful. Appendix B of the Granularity Document list a few examples on possible use like e.g. for Note to the Reviewer, cross-reference to Drug Master File or CEP, or a Control Strategy Summary document. Controlled Vocabulary for associated ContextOfUse is available. However, the actual section content besides the summary files should still be submitted at the lower level.

10.1.1 Granularity of Module 3.2.S

A change specific to Module 3.2.S is the elimination of headings 3.2.S.1.1 – 3. Note 4 tells the reason: "The lower level of each heading included in CTD-Q at this point is unlikely to contain individual documents or files." Consequently, Controlled Vocabulary is available for 3.2.S.1 level, but not for S.1.x anymore. Nevertheless, it is still possible to submit more than one document under this 3.2.S.1.

For section 3.2.S.7.3, eCTD v4.0 offers the opportunity to distinguish the stability data by an optional "descriptor" keyword; details are given in Appendix C of the Granularity Document. The Applicant may decide which values this keyword should have; this could be the site of manufacturing or a specific process or process scale, for example.

Apart from the Granularity Document as such, the extended lifecycle possibilities add a lot of flexibility to Dossier Planning and lifecycle management. Values of keywords can be changed and the ContextOfUse concept allows for rolling-up of formerly separate documents or splitting large documents into smaller ones. Therefore, the Applicant does not have to stick to the decision on dossier granularity for the initial submission any longer, but can reorganise it according to the needs during MAA assessment and follow-up procedures. Nevertheless, fundamental principles of Dossier planning as described in Chapter 6.1 remain valid with eCTD v4.0, too.

10.1.2 Granularity of Excipients Section 3.2.P.4

Like revised for eCTD v3.2.2 (see Chapter 9.6), too, documents can be placed either directly under heading 3.2.P.4 or at lower 3.2.P.4.x levels. A new ContextOfUse has been created to assign a document directly to heading 3.2.P.4.

Moreover, almost unlimited flexibility to organise this section in eCTD v4.0 is made possible. This is announced briefly but precisely in Appendix D of the revised Granularity Document [20]:

Applicants may choose a granularity that best suits their business needs and as appropriate for the application. All excipient data can be organised using one or multiple documents and within one or multiple Excipient sections.

At the time of initial submission, granularity can be chosen as deemed best for the review process. Later on, the ContextOfUse concept and the possibility to change values of the excipient keywords permit higher flexibility to address future changes of status or name of the excipient.

10.2 Analysis of Changes to Granularity with eCTD v4.0

The revised Granularity Document addresses a number of issues identified in the analyses in Chapter 7 and 9.6.

The split of 3.2.S.1 into three sub-level documents is no longer mandatory; even more, the subheadings have been removed from the ContextOfUse CV. Thus, three documents that are unlikely to have any life cycle at all for most drug substances, can now be rolled up to one.

The new "descriptor" keyword offers the possibility to better organise stability data. That way, stability data for drug substance from different batches, processes, or sites can be easily distinguished. Furthermore, document grouping allows even deeper granularity if desired, for example to supplement stability data during MAA assessment with results from a later testing point.

Similarly, by exploiting the ContextOfUse concept combined with self-defined document groups, additional granularity is achievable, e.g. for contents of Section 3.2.S.2 for complex substances.

For Section 3.2.P.4, in essence, solutions for all issues discussed in the Q72-Q75 for eCTD v3.2.2 have been implemented. Recommendation on when to use which granularity and how to organise lifecycle (see Chapter 9.5) has been transferred almost literally to Appendix D.

Overall, eCTD v4.0 improves the flexibility of granularity and lifecycle management for the whole dossier to an impressive extent. In case things in product lifecycle show up different than expected, decision on granularity at the time of initial submission now can be revised and the dossier can be adapted as needed for best presentation of the content. Nevertheless, it is still not permitted to submit an entire Module 3.2.S content in one document under heading 3.2.S, which would have been desirable for e.g. some ASMFs.

11 Conclusion and Outlook

Overall, current eCTD specification v3.2.2 and the revised Granularity Document are a reasonable compromise and provide a solid structure to start with building an MA dossier for the majority of drug substances. This sure is one of the reasons for the wide acceptance and ever-increasing use of eCTD.

The eCTD granularity and its basic option to either submit one or multiple documents under the respective heading largely works well for NCEs and, with some limitations, ASMFs. For well-known substances needing only little information in Module 3.2.S, which could easily be presented in just a single document, an option to roll-up the content under higher-level headings would be preferred. In contrast, for complex Biotech products a high volume of data is required, for which in some sections deeper CTD levels and eCTD attributes would be desirable.

Lifecycle issues primarily evolving from manufacturer changes can become annoying due to strict one-to-one exchange of documents and the impossibility to adapt eCTD attributes. Strategic dossier planning and some workarounds could limit such issues; however, unexpected scenarios might pop up anytime.

The recent revision of the Granularity Document does not solve the most urgent issues. Admittedly, most issues are inherent to the eCTD specification and can only be addressed with a revision of the specification itself. Nevertheless, some more flexibility like, e.g., rolling-up documents to higher eCTD levels was to be expected.

The advance of eCTD v4.0 and the recently published implementation documents promise solutions for the remaining issues by offering more flexibility of granularity and new concepts for improved lifecycle management.

eCTD v4.0 has the potential to finally succeed in offering both – Standardisation AND Flexibility.

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[20] ICH Guideline M4(R4), „Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use," 2016.

[21] „Meeting Report ICH Assembly 9 – 10 December 2015, Jacksonville, FL, USA, Item 20," 2016.

[22] CHMP, „Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product," 2007.

[23] eCTD IWG, „Question and Answer and Specification Change Request Document Version 1.27," 2015.

[24] ICH M8 EWG, „Electronic Common Technical Document (eCTD) v4.0 Implementation Guide v1.1," 2016.

[25] „HL7 Version 3 Standard: Regulated Studies; Regulated Product Submissions (RPS), Release 2," [Online]. Available: https://www.hl7.org/implement/standards/product_brief.cfm?product_id=38. [Accessed on 17 April 2016].

13 Appendices

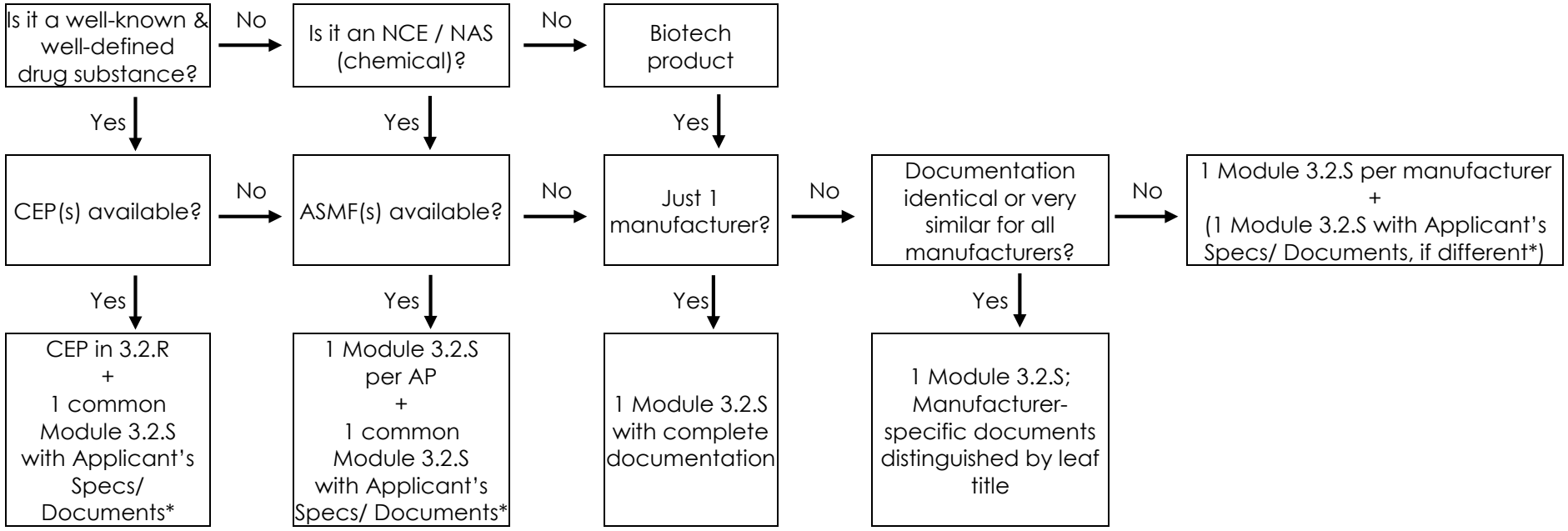
13.1 Common Post-approval Changes to Module 3.2.S

The table lists common post-approval changes [19] and those sections of Module 3.2.S, which are most likely affected by them. This is just a superficial and incomplete list and merely intended to be an aid for planning of dossier granularity.

Type of change	**Affected sections**
Addition/ Replacement of a manufacturer	Potentially new Module 3.2.S; also refer to App. 13.2
Minor changes in the manufacturer(s)	S.2.1, S.2.2
Minor changes in the manufacturing process	S.2.2, S.2.4
Major changes in the manufacturing process	S.2.x, S.4.x, S.7.x (A.1, A.2)
Changes in raw/starting materials	S.2.x, (S.4.x, S.7.x), (A.2)
Change in batch size	S.2.x, S.7.x
Changes to IPC	S.2.2, S.2.4
Change in the specification parameters (drug substance)	S.4.1, S.4.5, (S.4.2, S.4.3)
Change in the specification parameters (raw/starting material, intermediate)	S.2.3, S.2.4, S.2,5, (S,2,6), (S.4.4), (S.5), S.7.x, (A.2)
Change in test procedures	S.4.2, S.4.3, S.4.5, (S.2.x for raw/ starting materials)
Change in reference standard	S.5, (S.4.x)
Change related to Container Closure System	S.6, (S.3.2, S.4.x)
Change in storage period / conditions	S.7.x, (S.4.5)

13.2 Decision Tree for High-level Module 3.2.S Organisation

The figure depicts a basic approach to make a decision on the number of Modules 3.2.S for different types of drug substances and related documentation. However, before making a final decision on granularity, other aspects like lifecycle expectations or re-usability of the dossier for other regions should be considered, too.



* "Specs/ Documents" includes not only the Applicant's drug substance specification but any information, which are provided by the Applicant in addition to the documentation from the drug substance manufacturer(s) as well.

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