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Expectations of eCTD 4.0 – also a step forward for small and medium sized enterprises?

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

CP	Centralised Procedure
CTD	Common Technical Document
DCP	Decentralised Procedure
DTD	Document Type Definition
EC	European Community
eCTD	Electronic Common Technical Document
EMA	European Medicine Agency
ESTRI	Electronic Standards for the Transfer of Regulatory Information (ESTRI),
EU	European Union
EWG	Expert Working Group
FDA	Food and Drug Administration
HC	Health Canada
HTML	Hypertext Markup Language
ICH	International Council for Harmonization
LCM	Life Cycle Management
MAA	Marketing Authorization Application
MD5	MD5 Message-Digest Algorithm
MHLW	Ministry of Health, Labor and Welfare
MRP	Mutual Recognition Procedure
NeeS	Non-eCTD electronic submission
NP	National Procedure
PDF	Portable Document Format
PMDA	Pharmaceutical and Medical Devices Agency
RPS	Health Level Seven (HL7) standard
SME	Small and medium sized enterprises
STF	Study Tagging Files
TTM	Transition Mapping Message
UN	United Nations
USA	United States of America
WTO	World Trade Organization
XML	Extended Markup Language

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1 Introduction

Small and medium sized enterprises (SMEs) make up the vast majority of businesses in most countries. Both in Europe and the United States of America (USA) they are considered as the true backbone of economy - and this completely contrary to numerous perceptions abroad, which are essentially shaped by brands and names of large companies. In the European Union (EU) SMEs represent in general 99% of all businesses. In the past five years, they have created around 85% of new jobs and provided two-thirds of the total private sector employment in the EU. No wonder that they are considered as a major key to ensuring economic growth, innovation, job creation, and social integration.[1]

In the pharmaceutical sector SMEs are regarded as the motor of innovation and play a major role in the development of new medicines. For example, more than one in two medicines developed by SMEs that were recommended for marketing authorisation in the past ten years contained a new active substance. Due to their size these companies are considered to move or decide much more effective or creative than large pharmaceutical companies. On the other hand, they suffer from a lower financial cover which weakens their position vis-à-vis competitors. Employees of SMEs usually cover a much wider range of tasks than their colleagues in large enterprises. This inevitably results in a greater need for training or information on developments in the various areas in which these employees are working – with the challenge of a smaller financial budget.

However, an SME must react just as well and as quickly to changes in official requirements, e.g. in the regulatory area, as a larger competitor. In the regulatory area, this includes nowadays the changeover to and the daily handling of submissions with the electronic Common Technical Document (eCTD).

The development of the eCTD has been continuously advanced in the most important pharmaceutical markets since the beginning of the 21st century. Today eCTD is used as an international standard for submissions worldwide; development continues to progress. Currently eCTD v3.2.2 is being used, the next (major) step will be eCTD v4.0 approximately in 2020/21. Version v4.0 is considered a major update and will bring some fundamental changes for the user.

How will an SME deal with the features developed by the experts of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)? Are these all relevant for such a company at all? As already mentioned, SMEs make up a large proportion of companies in the pharmaceutical sector and seem to be therefore very important "customers" for the newly developed v.4.0 of the eCTD.

In this paper, an anonymous questionnaire has been developed to investigate which of the new features of eCTD v.4.0 are particularly interesting/useful for SMEs, what might pass by the needs of these companies and why. Next to the discussion of the results possible ideas or suggestions for a greater/another involvement of SMEs in further development directions of strategies of eCTD that may result from the results of the questionnaires will also be discussed.

[1] https://ec.europa.eu/growth/smes_de, accessed November, 1th, 2018.

2 Small and Medium sized enterprises

2.1 Definition

Small and medium-sized enterprises (SMEs) are defined in the EU recommendation 2003/361, as an example.[2] The abbreviation is used in the EU and also in international organizations like the World Trade Organization (WTO) or the United Nations (UN). The main factors determining whether an enterprise is an SME are (details see *Table 1*):

1. **staff headcount**
2. either **turnover** or **balance sheet total**

Table 1: Definition criteria for SMEs (m=million)

Company category	Staff headcount	Turnover	Balance sheet total
Medium sized	< 250	≤ € 50 m	≤ € 43 m
Small	< 50	≤ € 10 m	≤ € 10 m
Micro	< 10	≤ € 2 m	≤ € 2 m

Micro SMEs are by far the most common type of SME, accounting for 93.0 % of all enterprises and 93.2 % of all SMEs in the non-financial business sector.

However, micro SMEs account for only 29.8 % of total employment in the nonfinancial business sector, while small and medium-size SMEs accounted for 20.0 % and 16.7 % respectively of total employment.

In contrast to the very uneven distribution of the number of enterprises and employment across the three SME size classes, their contribution is broadly equal in terms of value added, ranging from 17.8 % (small SMEs) to 20.9 % (micro SMEs).

2.2 Role and meaning of SMEs for business

Despite their size SMEs are quite significant in different business areas, e.g. in the pharmaceutical and health industries. They outnumber large companies by a wide margin and also employ many more people.

They are a major source of entrepreneurial skills, innovation and employment.

All but 0.2 % of enterprises which operated in the 28 member states of EU in non-financial business sector in 2016 were SMEs. These SMEs employed 93 million people, accounting for 67 % of total employment in the EU-28 non-financial business sector and generating 57 % of value

[2] https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=uriserv:OJ.L_.2003.124.01.0036.01.DEU, accessed July 10th, 2018

added in the EU-28 non-financial business sector. Almost all (93 %) of the SMEs were micro SMEs employing less than 10 persons.[3]

> "Micro, small and medium-sized enterprises (SMEs) are the engine of the European economy. They are an essential source of jobs, create entrepreneurial spirit and innovation in the EU and are thus crucial for fostering competitiveness and employment." *(Günther Verheugen)*[4]

Due to their small size, SMEs are considered

- more effective (decision-making, hierarchy, lower employee turnover, intensive support, greater customer loyalty),
- leaner (hierarchy, costs),
- more creative (personal approach, good atmosphere) and
- more risk-taking

than large (pharmaceutical) companies.

On the other hand, they are often confronted with market imperfections. SMEs frequently have difficulties in obtaining capital or credit, particularly in the early start-up phase. High costs for licenses and in-house developments are a drain to the already restricted (financial) resources and can reduce access to new technologies or innovation or cause bottlenecks in other areas. They experience weaker positions vis-à-vis major competitors because of these structural weaknesses.

Nevertheless, SMEs are expected to continue their relatively steady pace of growth in 2017 and 2018, data from the EU.[5]

2.2.1 SMEs in the pharmaceutical sector (European Union)

A total of 1893 SMEs were registered at year end 2017 (*figure 1)*. This represents an increase of 5% compared to 2016.[6]

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[3] European Commission: Annual Report on SMEs, 2016/17, Executive summary. https://ec.europa.eu/growth/smes/business-friendly-environment/performance-review-2016_de, accessed November 10th, 2018

[4] Verheugen G in: The new SME definition, User guide and model declaration. https://www.eusmecentre.org.cn/sites/default/files/files/news/SME%20Definition.pdf, accessed November 10th, 2018

[5] European Commission: Annual Report on SMEs, 2016/17, focus on self-employment, https://ec.europa.eu/growth/smes/business-friendly-environment/performance-review-2016_de, accessed November 10th, 2018

[6] Annual Report SME Office 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/04/WC500247407.pdf, accessed November 10th, 2018

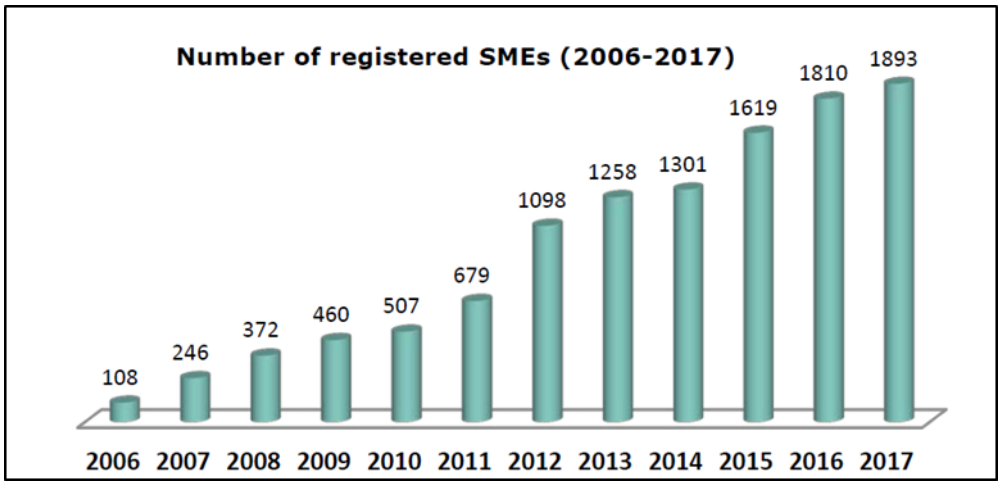

Figure 1: Number of registered SMEs (2006-2017)[7]

The distribution of SMEs in the pharmaceutical sector is consistent with the general figures for all sectors except the financial sector.

Most SMEs (40%) were micro- (<10 staff; turnover or balance sheet < € 2 mil), 35% small- (<50 staff; turnover or balance sheet < € 10 mil), and 25% medium-sized companies (<250 staff; turnover < € 50 mil or balance sheet < € 43 mil). The majority of the microsized companies is operating in Research and Development branch followed by academic spin-offs.

United Kingdom (17%), Germany (13%) and France (9%) show the highest density of SMEs. About one in ten companies was incorporated over the last three years (all over EU).

The large majority of companies are

- (bio)pharmaceutical companies developing or marketing medicinal products for human use (78%)
- veterinary medicines (4 %)
- products for both human and veterinary use (4 %)
- service providers to the pharmaceutical industry, e.g. regulatory consultancies, contract research organizations (14%).

About a fifth of SMEs operates in the medical devices area or has combined devices and medicines pipelines.

With regards to product pipelines, 12% of SMEs develop or market biologicals, 7% medicinal products for advanced therapies, 22% drugs for orphan diseases and 10% focus on paediatric solutions. Twenty three percent of companies develop or market generics.[8]

SMEs develop and market quite often only one or just a few products, across all business areas. In the pharmaceutical sector, an SME often sells also a product after successful development, but

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[7] European Union (EMA): SME office. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp, accessed November 10th, 2018

[8] Annual Report SME Office 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/04/WC500247407.pdf, accessed November 10th, 2018

before initial market approval. Or it only markets this product in some countries/regions, while others are licensed out.

2.2.1.1 Benefits

Various governments and institutions such as the European Medicine Agency (EMA) have long recognized the importance of SMEs. Among various incentives offered to SMEs in pharmaceutical sectors several are of high importance. Especially administrative and procedural assistance is appreciated. Moreover, fee reductions for e.g. scientific advice, scientific services and inspections and inclusion in the public SME register are also crucial. *Table 2* shows an overview of the assistances offered by important regions/countries in the pharmaceutical sector. *Note:* The benefits listed for Canada and Japan do not apply only to the pharmaceutical sector, but also to all business areas. Services especially offered by Health Canada (HC) or Japanese health authorities (Pharmaceutical and Medical Devices Agency (PMDA), Ministry of Health, Labour and Welfare (MHLW)) could not be found.

Table 2: Overview guidance for SMEs (per country/region)

Institution/ program	**Benefits**	**Country/ Region**
EMA SME office[9]	Direct assistance (phone, mail, telecom, meeting), fee exemptions/reductions, assistance with translations of product information (all EU languages) for initial MA, inclusion in online register, guidance on clinical data publication, liaison with academic investigators in pediatric medicine research, workshops, training sessions	European Union
FDA Small business assistance programs[10]	Technical assistance, exchange meetings, educational workshops, informational material, accessibility especially for SMEs for correspondence, information etc., grants/funding	USA
Health Canada Office of SMEs[11]	Financing, mentoring (with experienced business professionals), seminars	Canada
PMDA/MHLW SME Support[12]	Consulting service, mentoring (experienced business professionals), training programs, various information tools, funding, inclusion in register	Japan

[9] European Union (EMA): SME office. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp, accessed November 10th, 2018

[10] USA (FDA): Small business assistance: https://www.fda.gov/forindustry/smallbusinessassistance/default.htm, accessed November 10th, 2018

[11] Canada: Office of Small and medium sized enterprises: https://www.tpsgc-pwgsc.gc.ca/app-acq/pme-sme/index-eng.html, accessed November 10th, 2018

[12] Japan: SME support: http://www.smrj.go.jp/english/activities/, accessed November 10th, 2018.

2.2.1.2 Conclusion

When comparing the most important pharmaceutical markets in terms of SMEs, it becomes clear that promotional/supporting measures across countries/regions are very similar. They all attack where SMEs show weaknesses due to their size or structure. SMEs do not seem to have any region-specific characteristics; their characteristics are purely size- and structure-related. It could be assumed that the results of the present paper, which largely evaluated questionnaires from Germany and, to a lesser extent, Austria and the Netherlands, can therefore easily be transferred to other countries/regions.

3 Electronic Common Technical Document (eCTD)

3.1 History

The need to independently evaluate a medicinal product before it was released on the market was realized in different regions and different times. Real tragedies, like the Thalidomide occurence ("Contergan")[13] in the 1960ies, triggered the development of laws, regulations and guidelines for reporting and evaluating data on safety, quality and efficacy of new medicinal products. However, the divergence in technical requirements from country to country was still huge and took up lots of times to market medicinal products internationally.

The European Community (EC) pioneered in the 1980ies the harmonization of regulatory requirements. Using this measure on the one hand for establishing a single market for pharmaceuticals itself as well as a European Agency for the evaluation of medicinal products (Regulation (EC) No 726/2004[14]), the region demonstrated otherwise to the rest of the world that harmonization was feasible. As a consequence, the most important pharmaceutical markets (EC, Japan, USA) discussed joint regulatory-industry initiative on international harmonization; in the end The International Council for Harmonization (ICH) was conceived and incepted in 1990. The first topics of the new founded council included work on the development of a Common Technical Document (CTD).[15]

The term describes the organization of modules, sections and documents to be used by an applicant for a Marketing Authorization Application (MAA) for a medicinal product for human use in each of the European Union (EU), Japan and the US, a so called dossier. Harmonization was achieved with agreement on ICH Multidisciplinary Guideline M4: "Organization of the Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use". Nowadays this structure is common practice almost worldwide, not only in use in the three ICH regions.[16]

Since June 2003, applicants have the option of submitting an electronic Common Technical Document (eCTD) parallel to a paper submission (CTD) or Non-eCTD electronic submission (NeeS). Still varying are also submission routes, such as physical media, uploads to authorities via portals or mixed versions from the above. Starting in 2008/2009, the topic of harmonization and standardization of electronic submission is addressed by a so called M2 Expert Working Group (EWG).[17] ICH M2 task is currently the evaluation of new standards in the electronic area in general for its benefits and recommends the usage in the ICH context as appropriate. In 2010 the M8 EWG was built to deal with the specifics of eCTD.[18]

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[13] http://broughttolife.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide, accessed November 10th 2018

[14] http://apps.who.int/medicinedocs/en/d/Js17139e/, accessed November 1th 2018.

[15] https://www.ich.org/about/history.html, accessed November 1th 2018.

[16] https://www.ich.org/products/ctd.html, accessed November 1th 2018.

[17] https://www.ema.europa.eu/en/ich-m2-electronic-common-technical-document-ectd, accessed November 1th 2018.

[18] https://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html, accessed December 13th 2018.

Current ICH documentation on that topic is the ICH eCTD Specification Guideline M2 (v3.2.2).[19] Next step will be eCTD v4.0, to be implemented in the EU, USA, Canada and Japan approximately 2019/2010 (see section 3.3.1).

3.2 Structure

The harmonization of paper based dossiers submitted in different regions was one of the major topics addressed by ICH when deciding on the now common eCTD-structure. Furthermore, the form should reflect all future regulatory activities during a product/substance life cycle. The global agreement to use this structure has revolutionized the regulatory review process and made good review practices possible. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.[16] *Figure 2* shows the general structure of the eCTD. Only four of the five modules, modules 2-5, are part of the eCTD-structure, module 1 provides regional information.

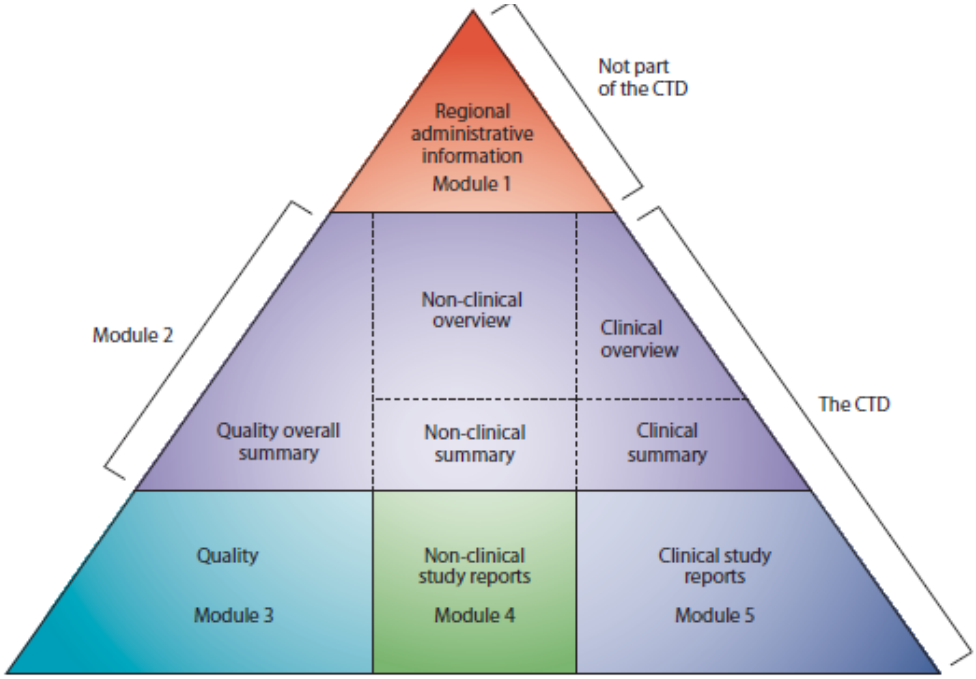

Figure 2: The eCTD triangle. The CTD is organized into five modules. Module 1 is region specific and modules 2-5 are intended to be common for all regions.**[16]**, modified

The structure, content and organization of module 1 are described in local specification files. Modules 2-5 are common for the ICH regions. In Module 2 nonclinical and clinical overviews as well as CTD-summaries are located. Quality is described in module 4, development data as nonclinical (Module 4) and clinical (Module 5) study reports can be found in the last two modules. Each is further divided into sections and subsections, also to a certain granularity defined by ICH.[16] Several ICH guidelines, created by ICH Expert Working Groups, give direction in further

[19] estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf, accessed November 1th 2018.

details, e.g. granularity or high level content: M4Q(R1)[20], M4S(R2)[21] and M4E(R1)[22]. Other ICH guidelines provide as well additional advice.[23]

The use of eCTD has greatly simplified the creation of a dossier and also reduced largely reworking the documentation according to different country/region requirements. Module 1 is subject to regional differentiation, otherwise the same dossier can be used in all ICH regions.

3.2.1 Features of an eCTD – v3.2.2

The three major features of an eCTD so far, looking upon current version 3.2.2, are the **directory structure**, the **individual files** and an **Extended Markup Language** (XML) backbone. XML means a non-proprietary computer language which ensures together with a "document-type-definition" (DTD) and a style sheet that the files/structure can be read on any computer system almost without further software; only an internet browser is needed. Both applicant as well as reviewer are able to access these files with a standard web browser. Unlike **Hypertext Markup Language** (HTML), XML can be adjusted to the needs of the user – so definition of tags for documents and structure using a DTD is possible.[24] Once structure and granularity are set, it will be used for future submissions as well.

> "The purpose of the XML back bone is two-fold: (1) to manage meta-data for the entire submission and each document within the submission and (2) to constitute a comprehensive table of contents and provide corresponding navigation aids. [25]

3.2.1.1 Stylesheet

The Stylesheet file contains information that ensures that the content of the submission can be made visible in a viewing tool or XML web browser. A content integrity check guarantees the completeness/rightness of the transmitted information from sender (e.g. applicant) to receiver (e.g. authorities). The output of the MD5 Message-Digest Algorithm (MD5) by Electronic Standards for the Transfer of Regulatory Information (ESTRI), colloquially referred to as "checksum", can verify that the file has not been altered in the historical archive of the regulatory authority and also can proof the integrity of each file by comparing the submitted checksum with the file and the computed one. Acceptable file formats can also be defined as follows.[26]

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[20] http://www.ich.org/products/ctd/ctdsingle/article/m4qr1-quality.html; accessed November 11th. 2018

[21] http://www.ich.org/products/ctd/ctdsingle/article/m4sr2-safety.html, accessed November 11th. 2018

[22] http://www.ich.org/products/ctd/ctdsingle/article/m4er1-efficacy.html, accessed November 11th. 2018

[23] https://www.ich.org/products/guidelines.html, accessed November 11th. 2018

[24] http://www.xmlobjective.com/what-is-the-difference-between-xml-and-html/, accessed November 11th, 2018

[25] https://www.ema.europa.eu/documents/scientific-guideline/ich-m-2-electronic-common-technical-document-e-ctd-step-5_en.pdf, accessed November 11th, 2018

[26] http://estri.ich.org/recommendations/ESTRI_Gateway_V3_0.pdf, accessed November 11th, 2018

3.2.1.2 Leaf elements

The life cycle management of an eCTD is facilitated by some additional terms. As defined by CTD granularity the individual files submitted in sections and subsections are called leaf elements. One or many documents can be a leaf and will be published as a single Portable Document Format (PDF) output file. To each leaf metadata are associated, to ensure placement in the XML structure as well to secure its life cycle management. The lifecycle of a leaf is managed by the so-called leaf operators: *New*, *append*, *replace* and *delete*. *New* – is a leaf element never submitted before, *append* - adds a leaf element with additional information to an existing leaf element, *replace* - removes a leaf element and replaces it by a new one with updated content and *delete* - removes a leaf element from the current life cycle, it is not replaced by new content, the document itself is no longer visible in an cumulative view, but can be accessed opening the respective sequence.[19] The *append* lifecycle operator, designed as a way for applicants to update content already submitted, is set for official elimination with the release of eCTD v4.0. The sunset should not have much of an impact at all as already today its use is discouraged.[27]

3.2.1.3 Metadata

Information about a submission, e.g. drug substance, dosage form, excipients, manufacturer, type of submission etc. are provided by metadata. This allows the documents and sections as well as their relationships to each other to be identified, thus creating a correct structure of submission. It also ensures a proper Life Cycle Management (LCM).

3.2.1.4 Node extensions/Study Tagging Files

Node extension support further the organization of the eCTD structure. They are also used as headings that go beyond the official ICH headings. But these extensions are not used in all regions/countries. Especially in Module 5, Study Tagging Files (STF) represent a second way of structuring.

3.3 Pro and Contra eCTD v.3.2.2

The eCTD, current version v3.2.2, meets the following requirements: good availability of the dossier, a straight forward viewing and good navigation functionality, the possibility of a quick overview of submitted dossiers and fast retrieval of the documentation including life cycle functionality both on the document and dossier level, meaning seeing the relationship of different sequences, and having the option to compare individual documents directly as described above. Last but not least a reduction of paper submissions was anticipated.[28] The mere fact of using the same structure in all regions/countries is a huge advantage itself.

But this development has also brought with it some disadvantages: For example, the granularity is defined early on with the first submissions. Changes are not really possible and lead to

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[27] http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v4%200-20160422-final.pdf, accessed November 111th, 2018.

[28] Dehmlow H: eCTD submissions: A global reality already? Masterthesis "Master of Drug Regulatory Affairs", Rheinische Friedrich-Wilhelms-Universität Bonn; 2016, 91 p (modified).

inflexibility in document life cycle management. Or deleting of documents might lead to invalid external hyperlinks.

A fixed DTD (see section 3.2.1) is not capable to allow changes to implement easily. Therefore, any change of a structural element or a change to metadata elements will require a new DTD for Module 2 to Module 5 or for Module 1, causing a huge investment to update the software and re-validate the installation. Furthermore, special tools for publishing the output of an eCTD as well as trained experts are necessary, resulting in further investments and costs for the company.

Many consider it a major disadvantage that communication from the authority is not reflected in the eCTD, only the communication from the applicant to the authority.[28]

Note: These are just a few examples to point out weaknesses or directions for further development, with no claim to completeness.

3.3.1 Next step – eCTD v4.0

3.3.1.1 History and outlook

Since the implementation of eCTD v3.2.2 numerous calls of change requests have been made. As a result of this M2 developed the next major version requirements in 2009. To address the enhancements to the eCTD specification, M8 EWG was formed in November 2010 to specifically focus on the development and implementation of eCTD v4.0. [29]

The main goal of upgrading to eCTD v4.0 is to facilitate the processing and review of electronic regulatory submissions. The following items are discussed in detail in other sections of this document, but are outlined below as they are the key business drivers for the next major version of eCTD:[30]

Document Reuse – the ability to submit a document once to a Regulatory Authority and refer to the document by its unique identifier in future submissions if the document is validly retained by the Regulatory Authority.

Document and Metadata life cycle – the ability to manage the versions of documents and/or metadata.

Management of Context Groups – the ability to group documents together based on nature of their use (e.g., components of clinical study reports)

[29] https://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html, accessed November 25th, 2018.

[30] http://estri.ich.org/new-eCTD/index.htm, accessed November 25th, 2018.

More in detail, eCTD v4.0 offers enhanced flexibility in regard to granularity of the content structure per single dossier as well as in general – able to implement new regulatory requirements without any change of software (DTD):[31]

- Options to accommodate regulatory changes without delay and major technical changes as content related changes can be achieved by updates of controlled vocabularies or modification of keywords

- Applicability of the same technology for all types of regulated products

- Use of controlled vocabularies to a wide extent

- Use of keywords to organize content

- Improvement of life cycle operations by simplification due to execution on the *contextOfUse*-element only

- Flexibility of dossier granularity and grouping of documents

- Assigning Submission Units to different applications by only referencing a submission ID and application ID

- Referencing documents across applications

- Re-use of documents

- Support for two-way communication (presumably at a later stage of implementation)

At the December 2015 ICH meeting, the ICH Assembly endorsed the Step 4 ICH eCTD v4.0 Implementation Package v1.0 and related files. The Package has been updated in response to the change requests and/or discussion within the EWG after its initial release. The latest version (v1.3) was endorsed by the ICH Assembly at the June 2018 ICH meeting.[30] *Table 3* provides an overview of the planned features of eCTD v4.0 compared to those of v3.2.2.

Table 3: Planned features of eCTD v4.0[28]

Topics	**eCTD v3.2.2**	**eCTD v4.0**
Following ICH CTD guidelines	✓	✓
Exchange Message	XML	XML
Electronic Message Standard	ICH specification (M2-M5), regional specification (M1)	RPS
Regional XML, DTD, schema	✓	One global set

[31] http://esubmission.ema.europa.eu/eCTD%20NMV/eCTD.html and http://esubmission.ema.europa.eu/ectd/EU_eCTDv4_0_Step5-ImplementationPackageasof20180921.zip, accessed November 23th, 2018.

Structure	Electronic ToC, XML backbone	Virtual ToC, visible in viewing tool
Reusability of documents	Within an application using reference leaves	Across applications, unique Doc-ID (UUID)
Document life cycle	✓	✓ (without leaf operator "*append*")
Metadata/attributes life cycle	Correction not possible	✓
Change of granularity	---	✓
Grouping of documents	---	✓
Controlled vocabularies	---	✓
Two-way communication	---	✓
Complexity	✓	Increased technical complexity
Status tracking of submission	---	✓
Transition of current content	✓	✓

eCTD v4.0 is based on the Health Level Seven (HL7) standard called RPS. The RPS standard is intended for broader use as compared to eCTD and beyond life sciences. It could also support submissions for medical devices, veterinary, and other regulated products, such as tobacco.

The ICH Implementation Guide describes a onetime transition from v3.2.2 to v4.0 based on the consolidated version of a dossier. In this way document elements can be referenced in the future according to the eCTD specification v4.0. A baseline can be filed for this; the applicant will have to file it prior to the so called Transition Mapping Message (TTM) if he wants to reuse documents (TTM is the message submitted from the applicant to regulator when the application needs to transition from v3.2.2 to eCTD v4.0 format during its life cycle).[32]

It is also possible to submit later, with a TTM. Only documents that are already in eCTD format v3.2.2 can be transferred. According to current guidance[33] baselines must not include large-volume modules like Modules 4 and 5. As the transition sequence has to be built by the applicant, transition timing seems to be a **business decision**. Features of eCTD v4.0 can be used only after successful transition. Presumably, the same rules on baselining can be applied as for the switch towards eCTD v3.2.2.[34]

Currently the timeframe for the implementation of the new standards doesn't seem to be exactly delimited. Due to EMA's relocation from London to Amsterdam, numerous long-term projects

[32] http://estri.ich.org/new-eCTD/eCTDv4_0_SupportDocumentation_v1_3.pdf, accessed December 13th, 2018.

[33] http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf supporting technical aspects and http://www.hma.eu/277.html supporting business aspects of building baselines, both accessed November 25th, 2018.

have already been postponed. Against this backdrop, one can rely indeed on the following statement[34] […*The use of eCTD v4.0 messages may be feasible from 2019 onwards for practical (training) use in a testing environment….],* testing seems to be possible as scheduled, but it remains questionable whether the currently specified implementation period of 2020/21 (or later) in the most important regions is more likely to be reality. Although only the EMA moves, this authority plays a key role in the implementation of eCTD v4.0. Other authorities will react simultaneously with it.

[34] http://esubmission.ema.europa.eu/tiges/docs/Annex%201%20on%20eCTD%20v4.0.pdf, accessed November 25th, 2018.

4 Methods

4.1 Questionnaire

To interview representatives of SMEs, a questionnaire with ten questions was designed; an explorative approach was chosen. When selecting the questions, only user-relevant new features of eCTD v.4.0 were taken into account, which should cover all areas mentioned in section 3.3.1.1. All completed questionnaires could be used for evaluation (n=12), none needed to be excluded because of wrong use. Based on the approach, it is assumed that the results are representative.

The questionnaire was sent to various receivers/mailings list from the regulatory area via the surveymonkey® tool, mainly in Germany, but also to a lesser extend in Austria and the Netherlands. All completed questionnaires are shown in *Annex 1*.

4.1.1 Questions

The questions asked are listed below, together with the introduction. All completed questionnaires are shown in *Annex 1*, the content and form of the invitation which was sent out by mail is shown in *Annex 2*.

4.1.1.1 Introduction to the questionnaire

"The introduction of eCTD v.4.0 is considered a major update that differs in many respects from the current version 3.2. The survey is focusing on changes affecting the companies, the so called "users" in the survey."

4.1.1.2 Question 1

Q: In which area of the pharmaceutical industry is your company located? (Only one selection possible)

A1: Biotech

A2: Herbal/Homeopathic

A3: Small molecules

A4: Biologicals

A5: Advanced Therapies

A6: Other

4.1.1.3 Question 2

Q: *How many employees are working in your company in the Regulatory affairs department?* (More than one selection possible)

A1: Up to two

A2: Up to five

A3: Up to ten

A4: The department is outsourced to some extent

A5: The department is outsourced completely

4.1.1.4 Question 3

At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/2021. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow in Europe. US authorities (Food and Drug Administration (FDA)) and most probably also Health Canada and PMDA/MLHW will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures.

Q: *When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often.* (More than one selection possible)

A1: European Union: Central Procedure

A2: European Union: Decentral Procedure

A3: European Union: Mutual Recognition

A4: National Procedures in the EU

A5: FDA

A6: Health Canada

A7: PMDA/MLHW

4.1.1.5 Question 4

Q: *When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring?* (Only one selection possible)

A1: My company will be an early adopter of the features of eCTD v.4.0

A2: We will most probably wait until all challenges have been fixed

4.1.1.6 Question 5

Q: *Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. the SME Office of EMA?* (More than one selection possible)

A1: I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.

A2: I welcomed the move towards electronic submission. But our company was a late adapter of various reasons. We experienced some difficulties and we still have some.

A3: I welcomed the move towards electronic submission. But our company was a late adapter of various reasons. We experienced some difficulties but now we are familiar with the process.

A4: We use or have used support provided by authorities especially for SMEs, Yes/No

4.1.1.7 Question 6

One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product. So there will be no more need to store files/reports in another/different filing system, no more lost time spent for searching or collecting files for new tasks. But staff needs to be prepared for that. Furthermore a larger amount of staff will have to access for example the publishing software to reach out to that information – license costs, IT environment….. or at least they will need access to a viewer.

Q: What is your opinion about that? (Only one selection possible)

A1: I consider this development more as a burden.

A2: This development is a definite advantage for me.

4.1.1.8 Question 7

With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications.

Q: *Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio?* (More than one selection possible)

A1: Yes, that is of interest to us, we can simplify our work processes because of that, our product structure fits.

A2: No, our product portfolio is too diverse

A3: No, we are using software, which already masters this function

4.1.1.9 Question 8

Q: *If you answered "Yes" in question Five, please indicate to what percentage of your products this applies:* (Only one selection possible)

A1: Up to 25 %

A2: Up to 50 %

A3: More than 50 %

4.1.1.10 Question 9

With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in the lifecycle/in the following sequences after the first mention. This will significantly change the review workflow and have also some impact on other workflows.

Q: *What do you think will change in your company and what/how do you need to plan ahead for that?* (More than one selection possible)

A1: Software requirements must be established to support the necessary overview on what has been submitted already to which authority

A2: Employees must be trained

A3: Business rules need to be modified

A4: Viewers for the publishing software/more licenses must be bought and installed

A5: Roles must be redefined

A6: Transition time support must be planned

A7: Extra costs for all of that must be calculated and provided

A8: The common repository must be established to allow proper referencing across applications

4.1.1.11 Question 10

With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity. Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.

Q: *So, how often do you need to make changes of the kind described and how useful do you rate this function?* (More than one selection possible).

A1: I often have to make changes and thereby have a lot of work

A2: I often have to make changes but thereby have little work since I use generic metadata (e.g. manufacturer I, manufacturer II, instead of "company name, address" for manufacturer)

A3: This new function seems to be useful for my tasks

A4: I think I will rarely need this function

A5: This function does not seem to be useful for my tasks

4.1.1.12 Additional remarks

In questions 2, 4-7 and 9-10 a free text field was included, with the heading "Please feel free to add something missing or comment". As this was a voluntary option and not all participants have completed this field, it is mentioned only in the corresponding subchapters of the overview diagrams and will be taken into account in individual cases in the discussion.

5 Results and Evaluation

5.1 Overview and distribution of participants (question 1)

A total number of twelve participants has been counted. Answers came from different areas in the pharmaceutical industry (*figure 3*). The largest group is in the biotech area, according with different opinions, which see in this area very many SMEs. Next are "Small Molecules", followed by "Biologicals" and "Advanced Therapies". Nobody took part from the Herbal/Homeopathic sector. Three participants chose "Others", these were "Radiopharmaceuticals", "API" (most probably a drug manufacturer), "bio equivalence" (most probably generic products) and one "consultant". All in all for a sample this small, it seems to be a diverse and satisfying distribution.

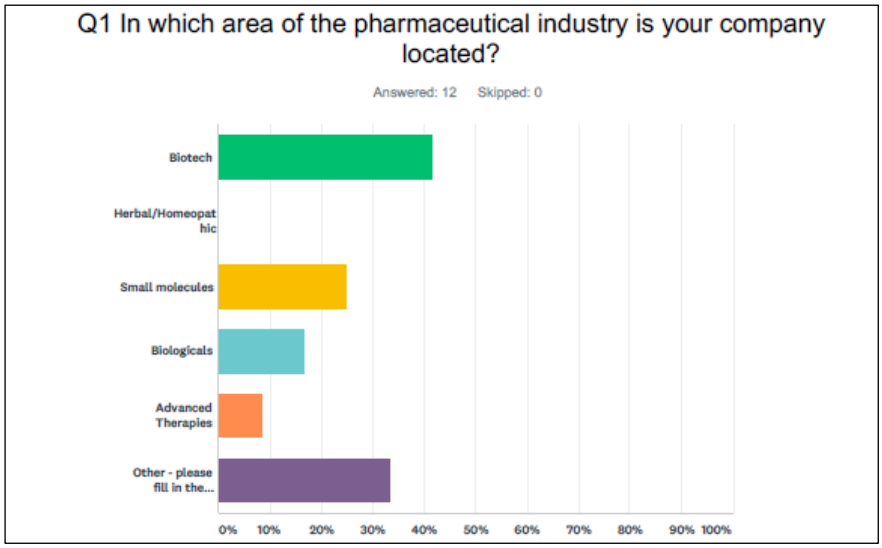


Figure 3: Participants by division (n=12)

5.2 Meaning of Regulatory Affairs department (question 2)

As already mentioned before, a lot fewer people work in a department of a SME compared to a larger company, at the same time staff/a role within a SME is covering a much broader range of tasks. Question two should give a first indication against this background of how well the SME is positioned in terms of Regulatory Affairs or in other words, how highly is this department valued for such a small company? (*figure 4*). At the same time it was asked whether and to what extent this very special department might have been outsourced.

Compared to total sizes of SMEs in the EU[8], three out of four micro- or small-sized with a staff under 10/under 50, a lot of value seems to be placed on the staffing of regulatory affairs department, looking at the figures given below (*figure 4*). At the same time, this department is completely or partially outsourced, at least in individual cases. It can be assumed that with external resources, probably some more staff will work in SMEs for Regulatory Affairs than the figures show. Two participants added comments, one was "eCTD publishing has been outsourced", the other commented "Way more employees", which reinforces this assumption.

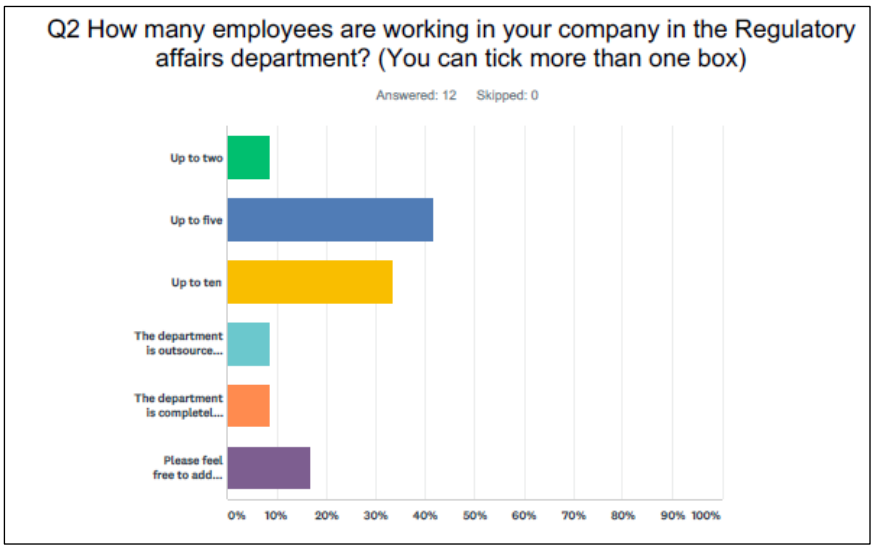


Figure 4: Meaning of Regulatory Affairs department, by staff counting (n=12)

5.3 Distribution of submission procedures (question 3)

From question three on the themes move slowly to individual features of eCTD v.4.0. Although almost all participants came from Germany (and the Netherlands and Austria), America's FDA is the most elected authority, closely followed by CPs in the EU. This does not come as a surprise; the US market is very important for European companies. The remaining possible EU procedures follow with equal percentages, on a par with Health Canada, most recently Japanese authorities (*figure 5*). Although CP ranks first within the EU procedures, it is clear that decentralised procedures are still relevant at least for SMEs.

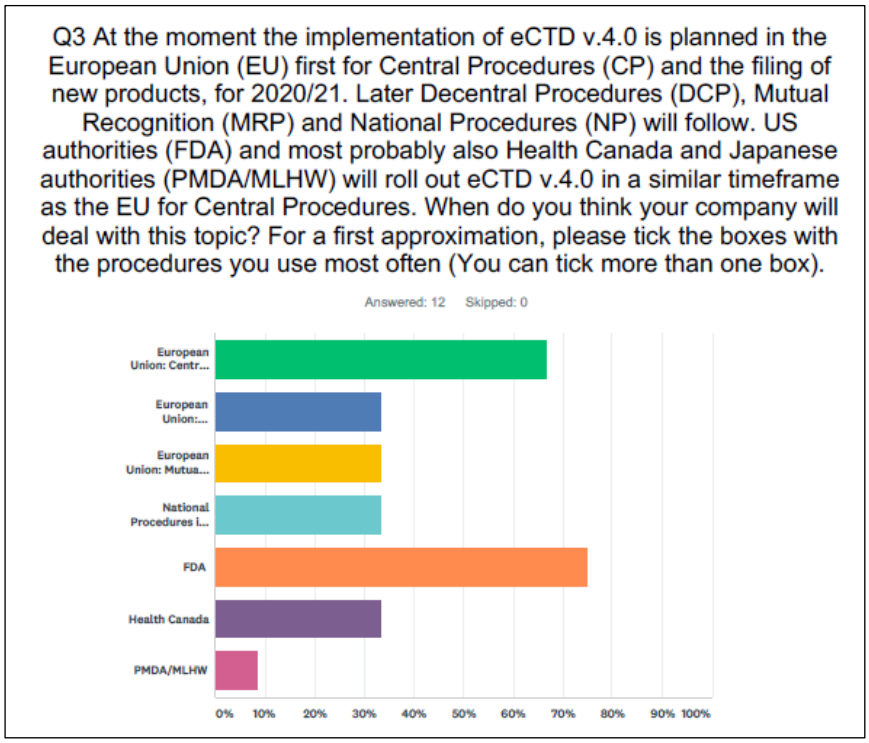


Figure 5: Distribution of submission procedures (n=12)

In the author's opinion the fact that Japan - one of the most important pharmaceutical markets, but quite a distant one for European companies - seems to play such an insignificant role here is due to the sample, which consists mainly of German SMEs (and other EU countries). It may also play a role that SMEs often market only one product or only a few at all themselves. Partnerships and licensing agreements in different (and more distant) countries can prevent, for example, a small European company from frequently submitting its own product(s) there itself. In addition, there is certainly a language barrier in a country like Japan present, compared to the US or Canada, against this background a local partner for submissions in such a country seems very attractive especially for an SME (see also section 2.2.1).

5.4 eCTD v4.0 – when to switch? (question 4)

eCTD v4.0 is considered a major update and will bring a lot of changes in different areas for all users. At the same time, experience has shown that such a step forward also contains most probably multiple errors due to the numerous changes and innovations. SMEs with their low financial resources can without any doubt afford less mistakes than comparatively large companies. The majority of the participants decided for a late transition to eCTD v4.0 (*figure 6*). One participant commented "as we have outsourced eCTD publishing we will be up-to-date", the company seems to rely on service providers or consultants to deal with this challenge.

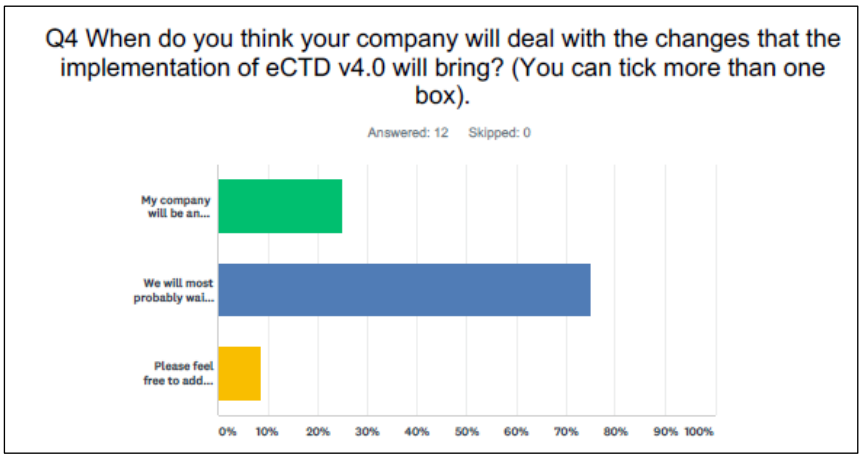


Figure 6: Opinions on the implementation of eCTD v4.0, target timeframe (n=12)

5.5 SME support and experience with eCTD (question 5)

For about 15 years, applicants have been able to submit dossiers electronically, at least in the ICH countries. This possibility also appears to have been accepted by SMEs, with 50% indicating that they switched to eCTD early. Some had difficulties in the beginning, but these seem to be solved, none of the respondents still has significant problems with electronic submissions. Only one participant has already requested support specifically for SMEs (*figure 7*). One commented "see above - it was outsourced".

This seemingly low demand for regulatory support is in line with the results of the current EMA Annual Report: Of 1893 SMEs registered in 2017, 184 sought regulatory support[8], about 10%, which is pretty much in line with the results of this survey. However, the nature of the support

was not more precisely addressed. The EMA report still shows figures for assistance with scientific advice or study protocols, but there is no indication as to whether these figures are already included in the general information on regulatory assistance.[8]

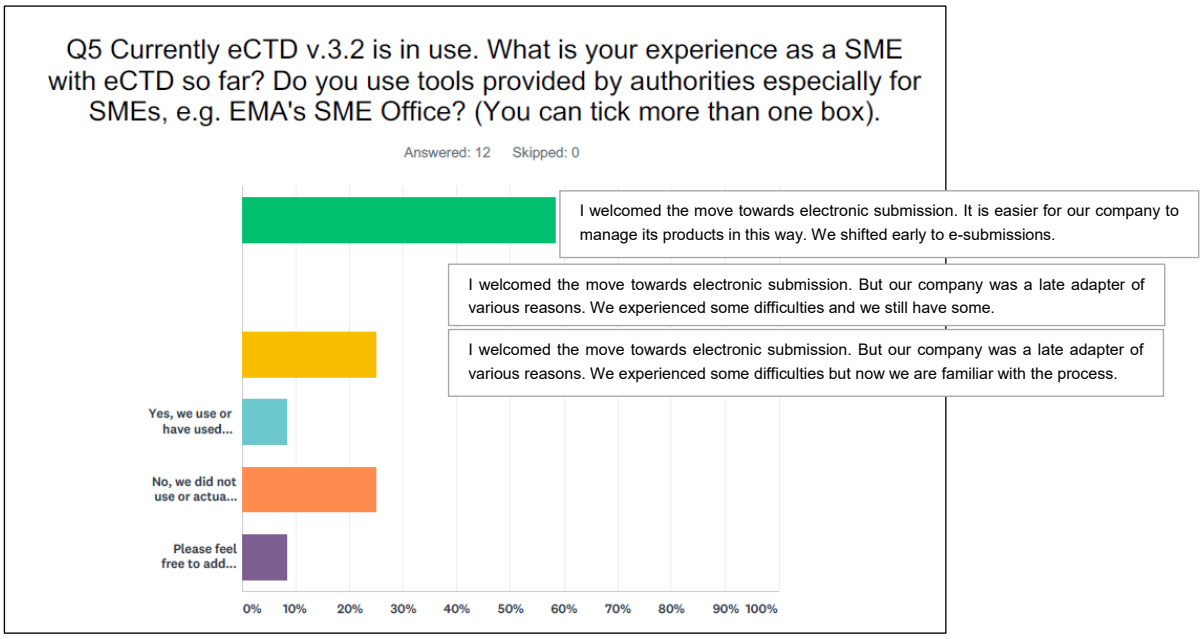


Figure 7: SME support and experience with eCTD so far (n=12)

Note: The labels of lines 1-3 are written out in detail on the right for reasons of comprehensibility

5.6 Features of eCTD v4.0: Two-way communication (question 6)

Until now, applicants have had to store authority responses in a separate document management or filing system; the current version v3.2.2 of the eCTD does not provide any space for this. Especially the innovation with v4.0, to be able to place authority responses in the lifecycle as well, seems to be a real labor saving and a progressive one. At the same time it will be necessary to fundamentally change many workflows in shift to eCTD v4.0. Nevertheless, majority of participants is looking forward to it (*figure 8*), but some are skeptical. One commented “don't know - let's see what will be the impact“, strengthening the sceptical group.

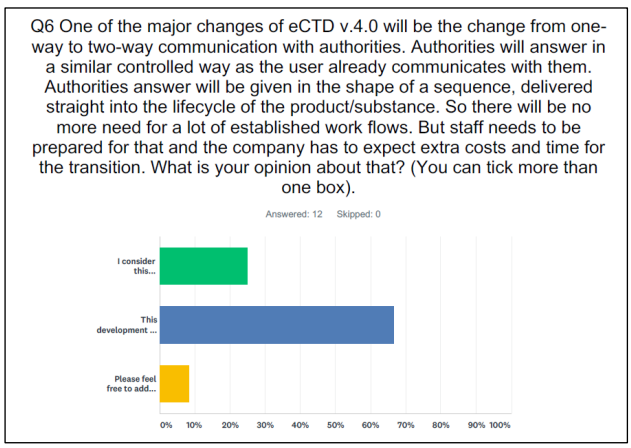


Figure 8: Opinions on eCTD v4.0: two-way communication (n=12)

5.7 Features of eCTD v4.0: Submissionunit-files (questions 7,8)

The possibility to control/update several lifecycles with one file seems to be of interest for most of the participants. But here two participants, one in a comment “I'm not up to speed on this but we already have instances where one file will point to multiple (locations in) applications” are already using software for this, for some the product portfolio is not suitable, and two more comment “Not yet of importance for the company” and “At the moment we have to manage only one product”. The last comment is certainly true for numerous SMEs and against the background that this question does not point to a clear trend (for SMEs, *figure 9*), this feature of eCTD v4.0 doesn't seem to be very relevant for (the majority of) SMEs, according to this survey.

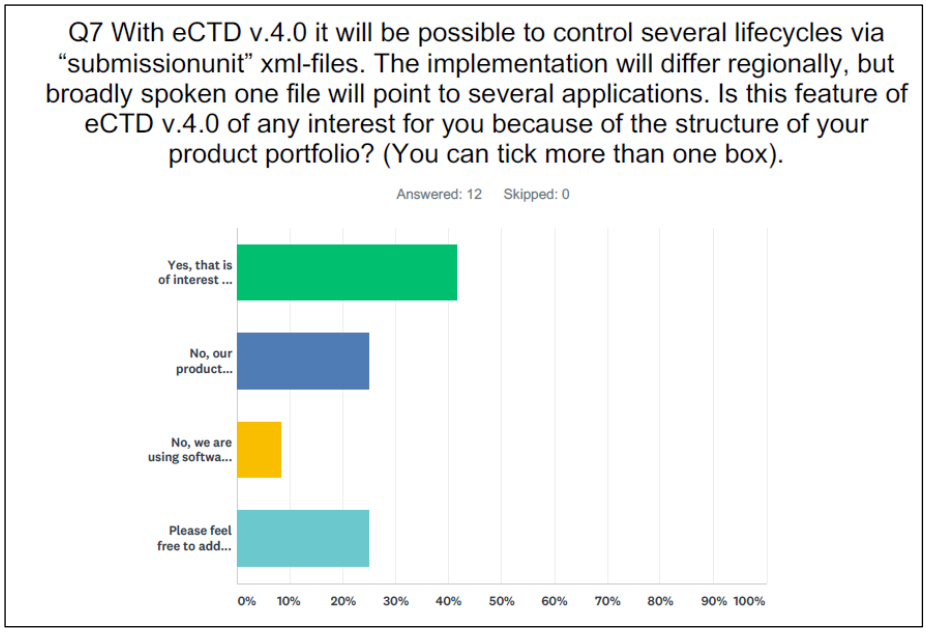


Figure 9: Opinions on eCTD v4.0: Submissionunit-files (n=12)

Nevertheless, approximately half and more of the product portfolio of the participants who answered in Q7 with “Yes” (about half of the participants) seems to apply (*figure 10*).

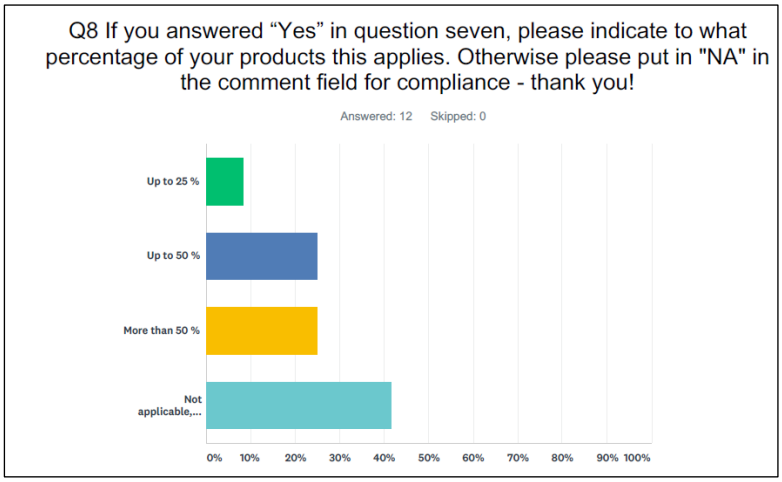


Figure 10: Opinions on eCTD v4.0: Submissionunit-files, details (n=12)

5.8 Features of eCTD v4.0: Universal Unique ID (UUID) (question 9)

If a document only needs to be saved once in the future because it can be clearly identified and controlled via UUID, numerous workflows become superfluous or have to undergo revision. The question offered a multitude of possible answers, as many areas are affected. However, for the majority of participants adequate staff preparation is most important, followed by sufficient (time) planning of the transition to eCTD v4.0 and appropriate software to map it all. Surprisingly, costs seem to play only a minor role, at least at the moment. This also includes the acquisition of viewers/additional licenses, also obviously not in focus (*figure 11*). Due to the similarity of the measures that become necessary in the transition to eCTD v4.0, statements on transition in general could also be made with the answers of this question.

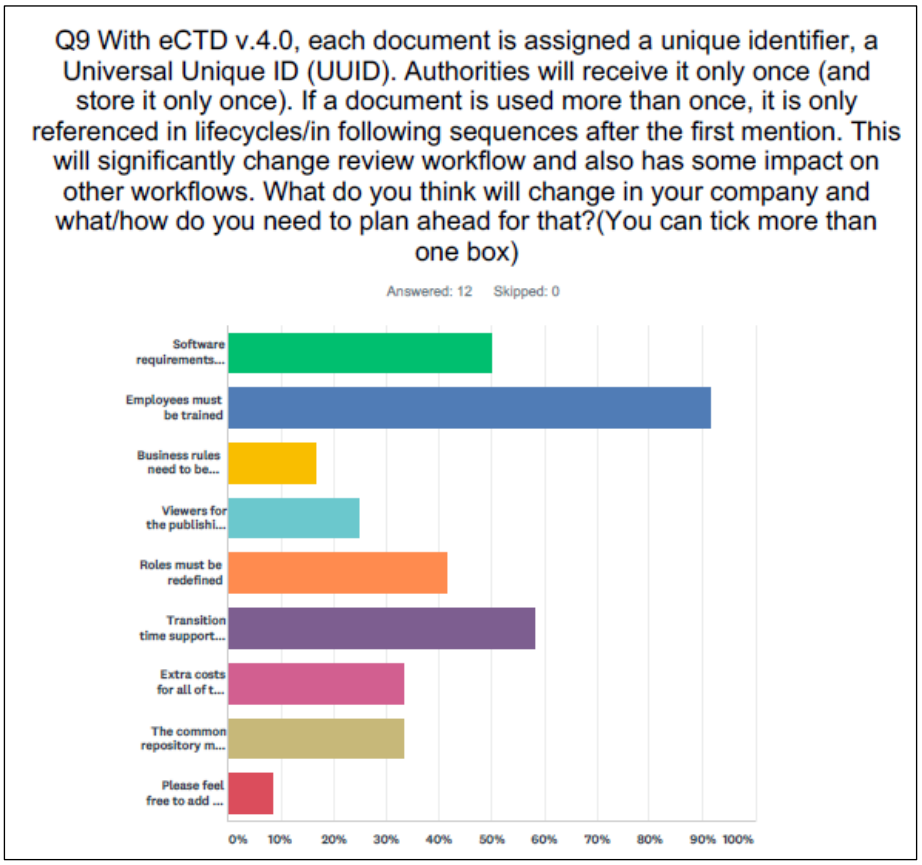


Figure 11: Opinions on eCTD v4.0: Universal Unique ID (UUID) (n=12)

5.9 Features of eCTD v4.0: Role of metadata (question 10)

In general the role of metadata is strengthened in eCTD v4.0. The majority of the participants welcomes this development, nevertheless about a third of them does not seem to need this feature or not to be able to use it. One commented “this is indeed a limitation in nowadays eCTD software, but some companies use workarounds that are not picked up by EiY” (*figure 10*).

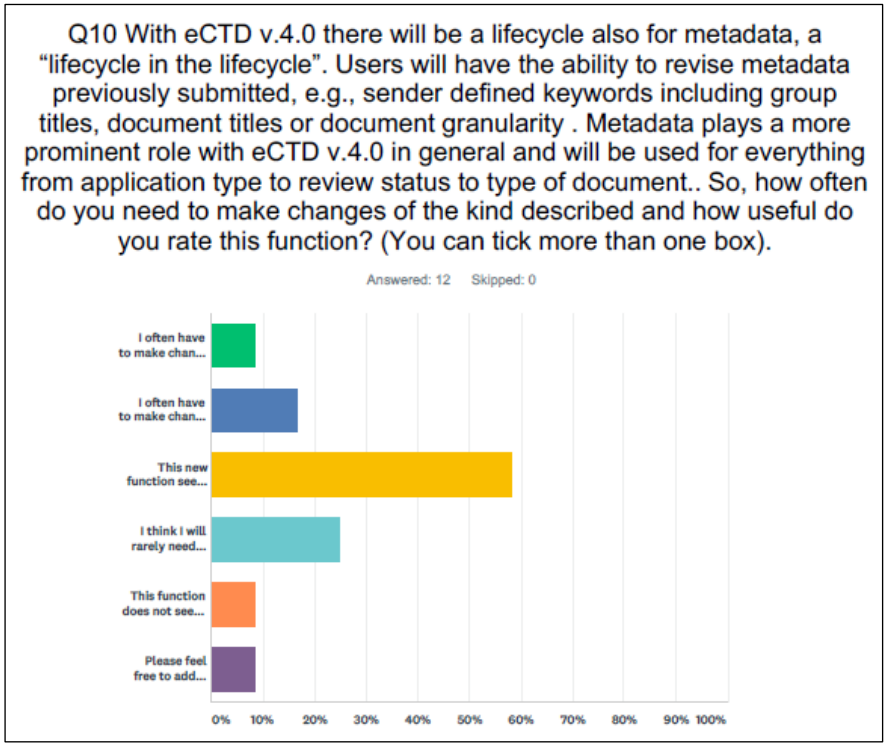


Figure 12: Opinions on eCTD v4.0: metadata (n=12)

6 Discussion

As eCTD is really used globally nowadays, even if not by all countries worldwide, it is easy to forget that it only began its career about 15 years ago. But it is, also the current v3.2.2, in many aspects still the result of the transformation into the electronic format. Surely a key of his success laid in the fact that the migration to the electronic format was easy to understand – it was and is not so different from his ancestor, the CTD. Therefore, only later disadvantages became noticeable, e.g. the strict granularity or inflexibility of the whole life cycle management. But this seemed some time ago a reasonable compromise because this transition has made it possible to take a major step towards harmonization and standardization of submissions. The fact that disadvantages of the eCTD became more and more noticeable only over the years can also be explained by that the requirements for accuracy and scope of the data to be submitted are becoming ever higher.

Stepping up to eCTD v4.0 is promising solutions to known weaknesses of eCTD v3.2.2. Although the transition process may be difficult, it has the potential to combine the already existing harmonization in v3.2.2 with flexibility for both applicants and authorities.

Nevertheless, the transition will be, among other things, associated with changes in many areas of work and additional (high) costs. Considered as a major step, many surprises can happen during the implementation of v4.0. The next years will be challenging ones for Regulatory Affairs data management, until the new version is fully operational.

This survey focused in particular on SMEs; how do they face electronic submissions on the one hand and how do they plan to deal with the introduction and new features of v4.0 on the other. Even though a truly satisfying distribution within the pharmaceutical sector could be achieved (question 1, see section 5.1), the total number of participants was only 12. Due to the explorative approach, this result of the survey is assumed to be representative. But because of the small number of participants, results and especially their interpretation should always be considered against the background that only a small sample led to it.

SMEs are able to deal well and quickly with changes, due to their structure. It is therefore no surprise that most participants were already in favour of the transition to eCTD and no longer seem to have any difficulty with electronic submissions (question 5, see section 5.5). Beyond that they already seem to be well informed about the new version, all questions were answered without any failures, no comments regarding misunderstanding etc.. However, even among SMEs, which are regarded as innovative motors in the pharmaceutical industry, there is a fundamentally wait-and-see tendency with regard to the implementation period of eCTD v4.0 (question 4, see section 5.4). This result is certainly due to the fact that there is not much information about the new version yet available. First tests will only be carried out next year. For comparison: The usage of eCTD v3.2.2 has taken about 8 to 10 years to get implemented - this will certainly play a role when deciding when to switch to v4.0, this may be still in the back of many minds. As already mentioned in section 3.3.1.1, it is a strictly business decision, made by the company.

In addition, SMEs can certainly not afford any major deficiencies in one direction, due to their tight financial covering. This may further influence decisions to look at new developments and directions reluctantly for the time being and only adopt them once the most issues have been eliminated. In the opinion of the author, this is not a specific tendency that only applies to eCTD

v4.0 - rather a common attitude of companies that can be observed in many areas, not only in Regulatory Affairs.

SMEs seems to value the Regulatory Affairs department, at least the participants (question 2, see section 5.2). Compared to the overall size, the department is well staffed. Although sometimes (partly) outsourced, Regulatory Affairs remains a part of the core business, which is carried out by the company itself. Against this background, it is not surprising that the most important measure to be untertaken to access properly for example the UUID-feature of v4.0 is "staff training"

In addition to staff preparation support during transition time as well as suitable software is similarly important for SMEs - which all can be extrapolated also for the transition to v4.0 in general (question 9, see section 5.8).

Costs - one would think that this point is particularly crucial for SMEs according to many opinions and analyses describing their financial scope. Financial support is included in every aid package that countries provide to SMEs (see section 2.2.1.1, *table 2*); the lower financial cover of these firms compared to bigger competitors is an essential structural feature. The question of costs, however, is only mentioned as the fifth most frequent in terms of dealing with eCTD v4.0 (question 9, see section 5.8). In the opinion of the author, this could be a further indication that the area of Regulatory Affairs is generally seen as a core business of companies and that it is therefore not influenced by cost-benefit calculations or budget cuts to the same extent as other departments.

The participating SMEs are giving way in terms of submissions in important pharmaceutical markets (USA, EU, Japan (Asia), Canada). Though without surprise FDA is the most frequently elected authority, followed by Central Procedures in the EU, but then HC and Decentralised/National Procedures in the EU follow on an equal footing with Japan as the tail light. However, many analyses see Japan as the second most important pharmaceutical market after the US.[35] The fact that Japan seems to play only a minor role, at least here in this survey, can be explained by a structural feature of SMEs: they are looking for partnerships to keep costs under control and to be able to jump cultural/language barriers, which can be difficult to master. It can be assumed that market access/approval in distant countries/regions such as Japan or Asia in general is often carried out by local partners and therefore no submissions are carried out by the company itself. Also it may have played a role that the participants were all from European countries.

The survey focussed on several user-relevant new features of eCTD v4.0 as well. Here opinions diverged: You can see a slight tendency towards agreement for all topics, but the answers remain diverse all over. Since implementation is not yet imminent, it can be assumed that most of the participants have probably not yet dealt with the details. Beyond that perhaps advantages of eCTD v4.0 are less relevant for SMEs in case they will submit messages for only a few products and don’t need to support a long-term life cycle (selling their products in an early stage of marketing, seeking partnership for licensing etc.) (questions 6-10, see section 5.6, 5.7, 5.8, 5.9, see section 2.1.1).

[35] https://www.fool.com/investing/general/2015/05/12/5-largest-markets-for-pharmaceuticals.aspx, accessed December 16th, 2018.

In summary one can assume that also SMEs are looking forward to the development of electronic submission standards and features. They seem up to date in terms of information and equipment - and on the other hand show a certain healthy scepticism to get involved quickly with new things. The answers to individual features of v4.0 were quite different, a clear tendency could not be seen in any question.

If you transfer the answers from the question to UUID on the transition time to eCTD v4.0 (question 9, see section 5.8), it may be possible to predict what seems to be important for SMEs during transition to v4.0 in general and what the critical points could be where they will need help. As staff training is mentioned most frequently, the provision of various training materials for personnel (e-learning, test environment for transit to eCTD v4.0, Q&A pages on authority websites (ICH, Health Authorities) at an early stage, increased support during transition) could be a possible option, cost-free or cost-reduced.

As it will be most probably necessary to develop and install new or adapted software/tools to allow a smooth transition to eCTD v4.0, like viewers, support for vendors can also be considered, for example.

Furthermore, authorities should be transparent about their implementation plans, keeping especially SMEs in the loop and at the same time informing them about special measures for SMEs. The EMA could, for example, do this by writing regularly to the SMEs listed in the EMA register, on the side an incentive itself for more companies to enroll.[36]

It is the author's opinion that due to the fact that SMEs are likely to wait with the transition to v4.0 like the majority of other companies, support around the actual transition phase is most crucial. For SMEs, this should mean a short intensive phase, as their product portfolio is often small and not very diverse. Due to their lean and effective structure, they could be valuable partners in the test phase of eCTD v4.0 and should be taken into consideration as these.

However, his survey, as small as it is, with all the question marks that result from it and with the still lengthy time span until the implementation of v4.0 in mind, shows at least tendencies that the future development of the eCTD could pass SMEs by. But Small and Medium sized Enterprises are after all the most common “species” in the pharmaceutical sector, they should be recognized and considered as this.

Involving representatives of SMEs more in future developments, bringing them in as members of expert groups perhaps or install them as fixed testing partners, could be next steps to meet the special needs of these companies, including a thorough stocktaking of needs.

Advantages of eCTD v4.0 for SMES could be found more in life cycle management, as it seems and generally spoken. The announced higher flexibility of granularity is in the authors opinion not so important for SMEs, due to their product portfolio structure. Surely SMEs will need special attention especially during transition time, otherwise eCTD v4.0 could become an additional burden for them rather than a benefit.

[36] https://fmapps.emea.europa.eu/SME/, accessed December 16th, 2018.

7 Summary

In this master thesis "Expectations of eCTD v4.0 – also a step forward to small and medium sized enterprises?" it has been examined with the help of a survey whether the planned introduction of eCTD v4.0 will be also an advantage for small and medium-sized enterprises (SMEs). The processing time was three months; it is the final thesis for the course of studies "Master of Drug Regulatory Affairs", author is Claudia Heidi Heß.

The eCTD is now used worldwide as the standardized form of dossier submission in the pharmaceutical sector. eCTD v4.0 is considered a major update compared to the current version v3.2.2. The new version brings amongst others some fundamental changes for the user. In summary, it can be said that the main features of v4.0 are greater flexibility in granularity and new concepts for improved life cycle management.

SMEs account for majority of enterprises in the pharmaceutical sector. Due to their size and structure, on the one hand they are considered to be more risk-friendly, more effective, leaner (hierarchy, costs) and more creative than large pharmaceutical companies; on the other hand, they suffer from a thin(er) financial cover, which can significantly restrict them in many areas. As an applicant, they are also regularly using eCTD for submissions to health authorities and have to respond as fast and secure as their competitors. The survey is intended to show whether the direction in which the eCTD is developing also suits SMEs, where questions should be raised or perhaps even a change of direction should be sought.

The survey only considers user-relevant features of eCTD v4.0; in addition, questions are asked about the company's Regulatory Affairs area and the division within the pharmaceutical sector. The participants, all SMEs, came from various sectors of the pharmaceutical sector and were recruited by e-mail via mailing lists, LinkedIn posts and personal contacts. The approach chosen for the evaluation is explorative.

Twelve fully completed questionnaires are included in the evaluations. The participants come from different areas of the pharmaceutical sector (Biotechnology, Biologicals, Advanced Therapies, Small Molecules, Generics, Consultancy, drug manufacture).

SMes are looking forward positively to the introduction of eCTD v4.0. The results show that small and medium-sized enterprises are also doing well with electronic submissions. Furthermore, SMEs see the further development of the eCTD towards v4.0 as positive.

But the questions on individual features of version 4.0 give very diverse answers. This fact and comments on this indicate that individual features such as the possibility to control different lifecycles with one file seem to be not quite relevant for SMEs.

Against this background first tendencies can be seen that the further development of eCTD may pass SMEs by, at least in this survey. Some suggestions are made to counter such a direction.

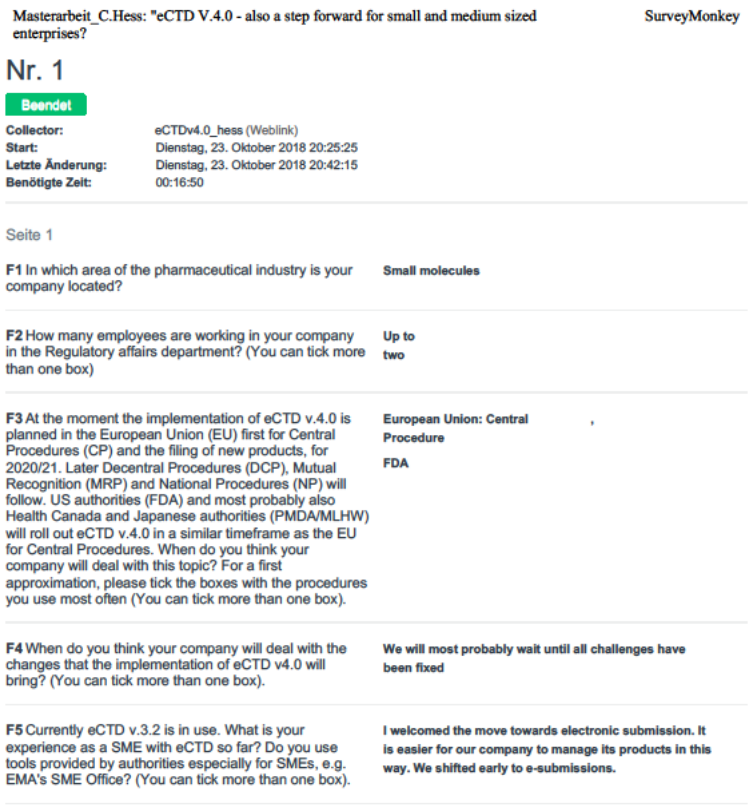
The thesis has a total of 61 pages, 2 Annexes

Annex

Annex 1

All questionnaires completed are shown, in the chronological order in which they were answered.

Participant 1:



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Nr. 1

Beendet

Collector:	eCTDv4.0_hess (Weblink)
Start:	Dienstag, 23. Oktober 2018 20:25:25
Letzte Änderung:	Dienstag, 23. Oktober 2018 20:42:15
Benötigte Zeit:	00:16:50

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Small molecules**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to two**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure** , **FDA**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.**

1 / 24

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	Please feel free to add something missing or comment.: At the moment we have to manage only one product.
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	Not applicable, please fill in "NA": NA
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Employees must be trained,** **Transition time support must be planned,** **Extra costs for all of that must be calculated and provided** , **The common repository must be established to allow proper referencing across applications**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This new function seems to be useful for my tasks**

Participant 2:

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Nr. 2

Beendet

Collector:	eCTDv4.0_hess (Weblink)
Start:	Donnerstag, 25. Oktober 2018 10:58:28
Letzte Änderung:	Donnerstag, 25. Oktober 2018 11:05:20
Benötigte Zeit:	00:06:52

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Advanced Therapies**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to ten**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure** , **FDA**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**No, we did not use or actually use support provided by authorities especially for SMEs**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	Please feel free to add something missing or comment.: Not yet of importance for the company
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	Not applicable, please fill in "NA": NA
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Software requirements must be established to support the necessary overview on what has been submitted already to which authority** , **Employees must be trained,** **Viewers for the publishing software/more licenses must be bought and installed** , **Roles must be redefined,** **Transition time support must be planned,** **Extra costs for all of that must be calculated and provided**

F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**I think I will rarely need this function**

Participant 3:

Nr. 3

Beendet

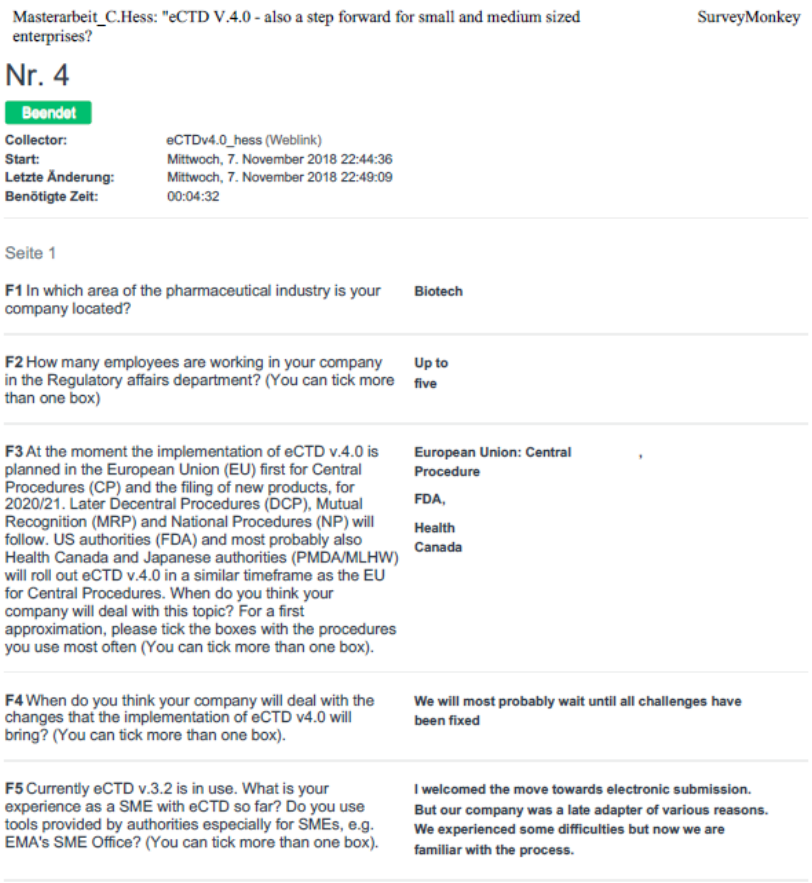
Collector:	eCTDv4.0_hess (Weblink)
Start:	Mittwoch, 7. November 2018 16:44:45
Letzte Änderung:	Mittwoch, 7. November 2018 16:50:30
Benötigte Zeit:	00:05:44

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	Other - please fill in the area.: API
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to ten**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure ,** **European Union: Decentral Procedure ,** **European Union: Mutual Recognition ,** **National Procedures in the EU,** **FDA,** **Health Canada**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**Yes, that is of interest to us, we can simplify our work processes because of that, our product structure fits**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**Up to 25 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Software requirements must be established to support the necessary overview on what has been submitted already to which authority ' Employees must be trained, Transition time support must be planned**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**I often have to make changes but thereby have little work since I use generic metadata (e.g. manufacturer I, manufacturer II, instead of "company name, address" for manufacturer)**

Participant 4:



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Nr. 4

Beendet

Collector: eCTDv4.0_hess (Weblink)
Start: Mittwoch, 7. November 2018 22:44:36
Letzte Änderung: Mittwoch, 7. November 2018 22:49:09
Benötigte Zeit: 00:04:32

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Biotech**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to five**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure** , **FDA,** **Health Canada**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. But our company was a late adapter of various reasons. We experienced some difficulties but now we are familiar with the process.**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**I consider this development more as a burden.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**Yes, that is of interest to us, we can simplify our work processes because of that, our product structure fits**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**Up to 50 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Employees must be trained,** **Roles must be redefined,** **Transition time support must be planned,** **Extra costs for all of that must be calculated and provided**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**I think I will rarely need this function**

Participant 5:

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Nr. 5

Beendet

Collector: eCTDv4.0_hess (Weblink)
Start: Donnerstag, 8. November 2018 16:16:56
Letzte Änderung: Donnerstag, 8. November 2018 16:18:25
Benötigte Zeit: 00:01:28

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Biotech**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**The department is completely outsourced**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**FDA**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**My company will be an early adopter of the features of eCTD v.4.0**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**I consider this development more as a burden.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**No, our product portfolio is too diverse**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**Up to 50 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Employees must be trained**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This new function seems to be useful for my tasks**

Participant 6:

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Nr. 6

Beendet

Collector: eCTDv4.0_hess (Weblink)
Start: Donnerstag, 8. November 2018 17:35:16
Letzte Änderung: Donnerstag, 8. November 2018 17:40:00
Benötigte Zeit: 00:04:44

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	Other - please fill in the area.: bio equivalence
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to five**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure ,** **European Union: Decentral Procedure ,** **European Union: Mutual Recognition ,** **National Procedures in the EU,** **FDA,** **Health Canada**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**My company will be an early adopter of the features of eCTD v.4.0**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**Yes, that is of interest to us, we can simplify our work processes because of that, our product structure fits**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**More than 50 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Software requirements must be established to support the necessary overview on what has been submitted already to which authority** , **Employees must be trained**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This new function seems to be useful for my tasks** , **I think I will rarely need this function**

Participant 7:

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

Nr. 7

Beendet

Collector:	eCTDv4.0_hess (Weblink)
Start:	Freitag, 9. November 2018 10:16:32
Letzte Änderung:	Freitag, 9. November 2018 10:27:27
Benötigte Zeit:	00:10:55

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Biotech,** **Small molecules,** **Biologicals**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to five**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure** , **FDA,** **Health Canada**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**Yes, that is of interest to us, we can simplify our work processes because of that, our product structure fits**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**More than 50 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Software requirements must be established to support the necessary overview on what has been submitted already to which authority** , **Employees must be trained,** **Viewers for the publishing software/more licenses must be bought and installed** , **Transition time support must be planned,** **The common repository must be established to allow proper referencing across applications**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**I often have to make changes but thereby have little work since I use generic metadata (e.g. manufacturer I, manufacturer II, instead of "company name, address" for manufacturer)** , **This new function seems to be useful for my tasks**

Participant 8:

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

Nr. 8

Beendet

Collector:	eCTDv4.0_hess (Weblink)
Start:	Freitag, 9. November 2018 13:31:04
Letzte Änderung:	Freitag, 9. November 2018 13:33:25
Benötigte Zeit:	00:02:21

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Biotech**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to ten**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**FDA**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. But our company was a late adapter of various reasons. We experienced some difficulties but now we are familiar with the process.** , **Yes, we use or have used support provided by authorities especially for SMEs**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**No, we are using software which already masters this function**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**More than 50 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Roles must be redefined**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This new function seems to be useful for my tasks**

Participant 9:

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

Nr. 9

Beendet

Collector: eCTDv4.0_hess (Weblink)
Start: Freitag, 9. November 2018 21:49:40
Letzte Änderung: Freitag, 9. November 2018 22:06:55
Benötigte Zeit: 00:17:15

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	**Small molecules**
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	Please feel free to add something missing or comment.: Way more employees
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Decentral Procedure** , **European Union: Mutual Recognition** , **National Procedures in the EU,** **PMDA/MLHW**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. But our company was a late adapter of various reasons. We experienced some difficulties but now we are familiar with the process.**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**No, our product portfolio is too diverse**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	Not applicable, please fill in "NA": NA
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Employees must be trained,** **The common repository must be established to allow proper referencing across applications**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This new function seems to be useful for my tasks**

Participant 10:

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

Nr. 10

Beendet

Collector: eCTDv4.0_hess (Weblink)
Start: Donnerstag, 6. Dezember 2018 08:10:05
Letzte Änderung: Donnerstag, 6. Dezember 2018 08:14:50
Benötigte Zeit: 00:04:44

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	Other - please fill in the area.: Radiopharmaceuticals
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to five**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Central Procedure**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**No, we did not use or actually use support provided by authorities especially for SMEs**

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**I consider this development more as a burden.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**Yes, that is of interest to us, we can simplify our work processes because of that, our product structure fits**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	**Up to 50 %**
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Software requirements must be established to support the necessary overview on what has been submitted already to which authority** , **Employees must be trained,** **Business rules need to be modified** , **Roles must be redefined,** **Transition time support must be planned**
F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This function does not seem to be useful for my tasks**

Participant 11:

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

Nr. 11

Beendet

Collector: eCTDv4.0_hess (Weblink)
Start: Donnerstag, 6. Dezember 2018 23:54:50
Letzte Änderung: Freitag, 7. Dezember 2018 00:04:35
Benötigte Zeit: 00:09:45

Seite 1

F1 In which area of the pharmaceutical industry is your company located?

Biotech,

Biologicals

F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)

Up to five ,

The department is outsourced to some extend ,

Please feel free to add something missing or comment.:

eCTD publishing has been outsourced

F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).

European Union: Central Procedure ,

FDA

F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).

My company will be an early adopter of the features of eCTD v.4.0

,

Please feel free to add something missing or comment.:

as we have outsourced eCTD publishing we will be up-to-date

F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.** , **No, we did not use or actually use support provided by authorities especially for SMEs** , Please feel free to add something missing or comment.: see above - it was outsourced
F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	Please feel free to add something missing or comment.: don't know - let's see what will be the impact
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	Please feel free to add something missing or comment.: I'm not up to speed on this but we already have instances where one file will point to multiple (locations in) applications
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	Not applicable, please fill in "NA": N.A. Don't know
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Employees must be trained,** Please feel free to add an aspect missing above.: Don't understand - isn't this already the current best practice?

F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**This new function seems to be useful for my tasks** , Please feel free to add something missing or comment.: this is indeed a limitation in nowadays eCTD software, but some companies use workarounds that are not picked up by EIY

Nr. 12

Beendet

Collector:	eCTDv4.0_hess (Weblink)
Start:	Dienstag, 11. Dezember 2018 15:02:09
Letzte Änderung:	Dienstag, 11. Dezember 2018 15:17:00
Benötigte Zeit:	00:14:51

Seite 1

F1 In which area of the pharmaceutical industry is your company located?	Other - please fill in the area.: consultants
F2 How many employees are working in your company in the Regulatory affairs department? (You can tick more than one box)	**Up to ten**
F3 At the moment the implementation of eCTD v.4.0 is planned in the European Union (EU) first for Central Procedures (CP) and the filing of new products, for 2020/21. Later Decentral Procedures (DCP), Mutual Recognition (MRP) and National Procedures (NP) will follow. US authorities (FDA) and most probably also Health Canada and Japanese authorities (PMDA/MLHW) will roll out eCTD v.4.0 in a similar timeframe as the EU for Central Procedures. When do you think your company will deal with this topic? For a first approximation, please tick the boxes with the procedures you use most often (You can tick more than one box).	**European Union: Decentral Procedure** , **European Union: Mutual Recognition** , **National Procedures in the EU**
F4 When do you think your company will deal with the changes that the implementation of eCTD v4.0 will bring? (You can tick more than one box).	**We will most probably wait until all challenges have been fixed**
F5 Currently eCTD v.3.2 is in use. What is your experience as a SME with eCTD so far? Do you use tools provided by authorities especially for SMEs, e.g. EMA's SME Office? (You can tick more than one box).	**I welcomed the move towards electronic submission. It is easier for our company to manage its products in this way. We shifted early to e-submissions.**

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

F6 One of the major changes of eCTD v.4.0 will be the change from one-way to two-way communication with authorities. Authorities will answer in a similar controlled way as the user already communicates with them. Authorities answer will be given in the shape of a sequence, delivered straight into the lifecycle of the product/substance. So there will be no more need for a lot of established work flows. But staff needs to be prepared for that and the company has to expect extra costs and time for the transition. What is your opinion about that? (You can tick more than one box).	**This development is a definite advantage for me.**
F7 With eCTD v.4.0 it will be possible to control several lifecycles via "submissionunit" xml-files. The implementation will differ regionally, but broadly spoken one file will point to several applications. Is this feature of eCTD v.4.0 of any interest for you because of the structure of your product portfolio? (You can tick more than one box).	**No, our product portfolio is too diverse**
F8 If you answered "Yes" in question seven, please indicate to what percentage of your products this applies. Otherwise please put in "NA" in the comment field for compliance - thank you!	Not applicable, please fill in "NA": NA
F9 With eCTD v.4.0, each document is assigned a unique identifier, a Universal Unique ID (UUID). Authorities will receive it only once (and store it only once). If a document is used more than once, it is only referenced in lifecycles/in following sequences after the first mention. This will significantly change review workflow and also has some impact on other workflows. What do you think will change in your company and what/how do you need to plan ahead for that?(You can tick more than one box)	**Software requirements must be established to support the necessary overview on what has been submitted already to which authority** **,** **Employees must be trained,** **Business rules need to be modified ,** **Viewers for the publishing software/more licenses must be bought and installed** **,** **Roles must be redefined,** **Transition time support must be planned,** **Extra costs for all of that must be calculated and provided** **,** **The common repository must be established to allow proper referencing across applications**

Masterarbeit_C.Hess: "eCTD V.4.0 - also a step forward for small and medium sized enterprises? SurveyMonkey

F10 With eCTD v.4.0 there will be a lifecycle also for metadata, a "lifecycle in the lifecycle". Users will have the ability to revise metadata previously submitted, e.g., sender defined keywords including group titles, document titles or document granularity . Metadata plays a more prominent role with eCTD v.4.0 in general and will be used for everything from application type to review status to type of document.. So, how often do you need to make changes of the kind described and how useful do you rate this function? (You can tick more than one box).	**I often have to make changes and thereby have a lot of work**

Annex 2

Mail how it was sent out to various mail distribution lists/LinkedIn Followers:

……

Subject: Survey for Masterthesis Drug Regulatory Affairs: eCTD v4.0 – also a step forward for small and medium sized enterprises ?

Dear receiver of this mail distribution list,

I would like to introduce myself first. My name is Claudia Heß, currently employed at Pharmalex GmbH, and I am currently writing my masterthesis in the degree programme "Master of Drug Regulatory affairs". The title is „eCTD v4.0 – also a step forward for small and medium sized enterprises?

You received this mail because my colleague Karl-Heinz Loebel kindly agreed to send the survey via this mailing list. It will also reach out to some active ingredient manufacturers. (this section has been varied according to the type of broadcast)

To evaluate the impact of the implementation of eCTD v.4.0 and the major changes it will most probably have especially on small and medium sized enterprises, I conducted a short survey. I would be most thankful if you would take the time and answer the questions assembled in in, ***if you are working for/in a small or medium sized company.***

Small and medium-sized enterprises (SMEs) are defined in the EU recommendation 2003/361. The main factors determining whether an enterprise is an SME are:

1. ***staff headcount***
2. *either* ***turnover*** *or* ***balance sheet total***

So, for your orientation: (m= Million)

Company category	***Staff headcount***	***Turnover*** *or* ***Balance sheet total***
Medium-sized	*< 250*	*≤ € 50 m* *≤ € 43 m*
Small	*< 50*	*≤ € 10 m* *≤ € 10 m*
Micro	*< 10*	*≤ € 2 m* *≤ € 2 m*

Please follow the link given below to the survey, if you said yes to a factor given above:

link to survey monkey

Please do not hesitate to call me via this mail adress if there are any questions.

Thanks a lot and kind regards

Claudia Heß (Mail: Claudia.H.Hess@web.de)

…….

Affidavit

"Hereby I, Dr. Claudia Heidi Heß, declare in lieu of oath that I have written the present paper independently and have used no other sources and aids than those indicated."

Place, date, signature

……..