

# Evaluating the Process of the Pattern Change from Paper based to Electronic Submissions of Medicinal Products

Scientifically based analysis of the advantages and disadvantages of the electronic Common Technical Document (eCTD) in Europe and North America

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This article is a summary of an empirical social research in form of an e-mail expert interview regarding the change from a paper based to an eCTD based electronic-only submission process in Europe and North America.

Eight international experts were asked about the advantages and disadvantages of eCTD submissions, and they were consolidated in eight different categories each.

Additionally potential reasons for or against an implementation of new eCTD processes were analyzed. The article ends with a short summary and conclusion and a remarkable expert statement regarding the consistency of eCTD for industry and authorities.

## 1. Why a scientifically based analysis of the advantages and disadvantages of eCTD does make sense

Since July 2003 the Common Technical Document (CTD) guidance, finalized by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), is

mandatory as the submission standard for medicinal products between pharmaceutical industry and agencies in Europe (NCAs<sup>1)</sup> and EMEA<sup>2)</sup> and is highly recommended by the U.S. Food and Drug Administration (FDA). At the time, the development of an electronic version of the CTD, called electronic Common Technical Document (eCTD), was already discussed and planned to be implemented in the near future. However, no fixed schedule was agreed upon.

In 2008 the FDA started to mandate the eCTD format for all electronic submissions to CDER<sup>3)</sup>, and the EMEA announced that eCTD will be required<sup>4)</sup> as of the 1<sup>st</sup> of January 2010. Additionally a few European NCAs already began to require fully electronic (eCTD only) submission process.

On the other hand, only some eCTD innovators and early adopters<sup>5)</sup> implemented the eCTD approach. Why is that? Because it is an immense change from a well known and adequate paper based process to a new unknown and potentially risky electronic-only process.

However, more and more agencies are mandating the new eCTD standard, and the pharmaceutical companies will have to implement eCTD, without evaluating the advantages and disadvantages. Therefore, most of them wait as long as possible to implement the new standard. This would likely change if the pros and

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<sup>1)</sup> National Competent Authorities (NCA).

<sup>2)</sup> European Medicines Agency (EMA); <http://www.emea.europa.eu/>

<sup>3)</sup> Center for Drug Evaluation and Research (CDER).

<sup>4)</sup> Directive 572459/2008.

<sup>5)</sup> Applied Clinical Trials (online), June 1, 2009.

■ Table 1

Experts selected for the qualitative research.

No.	Name	Company	Title	Country	Abbrev.
1	Karl-Heinz Loebel	PharmaLex	Head of Regulatory Operations	Germany	KHL
2	Hans van Bruggen	eCTDconsultancy	Senior Regulatory Affairs Consultant and Founder	The Netherlands	HvB
3	Harv Martens	ING America (acquired by EXTEDO)	Founder and member of the ICH M2 standards committee	USA	HaM
4	Sven Harmsen	E-DRA	Senior Consultant and Founder	Germany	SvH
5	Ted Hanebach	CanReg	Director Regulatory Standards	Canada	TED
6	Antoinette Azevedo	e-SubmissionsSolutions	CEO and Founder	USA	AnA
7	Dr. Gerhard Neurauter	EXTEDO	Managing Consultant and Product Manager	Germany	DrN
8	Katrin Spaepen	Comply Services	Managing Director and Founder	Belgium	KaS

cons of eCTD were made clear to the pharmaceutical companies and if the advantages would exceed the disadvantages.

The following qualitative research and scientifically based analysis of the advantages and disadvantages of eCTD will provide a basis for such a decision.

## 2. Scientific approach

The first of two methods of the empirical social research was an expert interview following the Delphi method – the qualitative part. It is an iterative process to collect and distill the anonymous judgments of experts using a series of data collection and analysis techniques interspersed with feedback. The Delphi method is well suited as a research instrument when there is incomplete knowledge about a problem or phenomenon<sup>6)</sup>.

Following this will be an online survey to enlarge and interpret the given answers of the qualitative research – the quantitative part.

<sup>6)</sup> <http://jite.org/documents/Vol6/JITEv6p001-021Skulmoski212.pdf>; 08. 08. 2009.

## 3. Qualitative research

### ■ 3.1 Selection of the experts

The experts listed in Table 1 were selected for the e-mail expert interview because of three main reasons. All of them

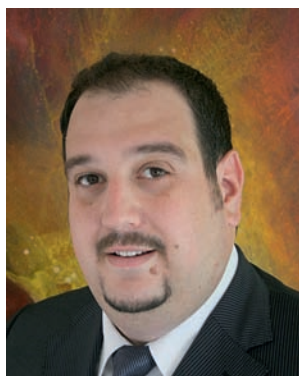
a) are consultants to pharmaceutical industry and agencies or are

affiliated to vendors and/or members of standardisation bodies

b) are located in Europe or North America

c) have proven experience in several eCTD electronic submissions to the FDA, EMEA, NCAs and others

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### ■ 3.2 eCTD advantages

The first question of the e-mail expert interview was:

*What are the advantages of electronic submissions in eCTD format?*

All relevant answers to that question could be pooled in 8 categories and are sorted by the number of experts giving the same or similar answers as follows:

- Stands for nearly the same answer as the category title
- + Stands for additional answers summarized in the category

#### I) Less paper, handling, logistic and archiving costs (6 out of 8 experts)

- Reduction of paperwork, including reduced costs for assembling binders and shipping (KHL)
- Save the cost of printing, shipping and storing paper (HaM)
- Save costs because paper does not need to be produced anymore (SVH)
- Eliminating the cost of handling, shipping, etc. paper (AnA)
- Reduction of handling and printing of paper (DrN)
- Reduced print costs and reduced logistics – also courier (KaS)

#### II) Less time to market (5 out of 8 experts)

- + Less time on the critical path if implemented properly (HvB)
- + Easy access to submission content to respond promptly to reviewer questions (HaM)
- Save time to market (SvH)
- + Allows for improved communication on the sponsor–agency levels (TED)
- + Speed of compilation after receipt of final documents. (AnA)

#### III) Life cycle and post approval maintenance (positive) (5 out of 8 experts)

- + Updates to initial submission are much more efficient – only the changed information is sent by the sponsor and automatically merged into the entire application at the agency (HaM)

- Simpler life cycle management (SvH)
- + eCTD format allows for the management of changes to the content and to the content status, throughout the life cycle of the product (TED)
- Ability to ... manage complex life cycle (DrN)
- + Electronic workflow (LCM) possibility (DrN)
- Life cycle management is “easier”, only the changed documents needs to be submitted (KaS)

#### IV) New processes (positive) (5 out of 8 experts)

- + Publishing eCTDs involves streamlining of business processes to a certain extent. A demanding task to most applicants, but in the long run it results in cost reduction, without loss of quality (KHL)
- + The CTD/eCTD standards provide a framework for managing drug development information from the laboratory to final submission (HaM)
- + Streamline internal authoring process (SvH)
- + More organized and controlled content preparation ... (TED)
- + Once eCTD process is implemented, the company may see a significant improvement in submission preparation cost efficiency (TED)
- + Harmonization of the regulatory process (DrN)

#### V) Findable content/data and reuse (5 out of 8 experts)

- + Optimal reusability of information ... (HvB)
- Easy access to submission content ... (HaM)
- + Data search and comparison. Pre-defined organization of files and detailed file, section and submission description (metadata) allows searching and data mining across sections and submissions (TED)
- eCTD standards allows re-use of content across different submissions (TED)

- + Allows for utilization of other standards within the submission process (SPL, PIM, CDISC standards ...) (TED)
- + Ability to show relationships between dossiers ... (DrN)
- + Improvements in ease of access and assessment of data (DrN)
- + Ability to see at any time the current documentation for a product (DrN)
- Reusability of submissions when in eCTD format (cloning) (KaS)

#### VI) Regulatory compliance (4 out of 8 experts)

- + ... better transparency of documents and dossiers, leading to a more efficient regulatory compliance (HvB)
- + More organized and controlled content preparation and submission compilation, which results in much greater quality of the content (TED)
- + Standardization and harmonization of information provided (DrN)
- + Automation and standardization of some administrative tasks (DrN)
- + eCTD submission quality is infinitely better than any paper submission (KaS)

#### VII) Transfer (agencies, partners and customers) (4 out of 8 experts)

- + ... to respond promptly to reviewer questions (HaM)
- + Organized information transfer (common transfer language between sponsor and regulatory agency) (TED)
  - Allows for efficient transfer of information through the gateways
  - Allows for improved communication on the sponsor–agency and agency–agency levels (TED)
- + Speed of transmission of eCTD to FDA thru FDA Electronic Submission Gateway (AnA)
- + Facilitation of the automatic transfer of data to external EU sources (DrN)

**VIII) Dossier navigation and improved preparation****(4 out of 8 experts)**

- + The ease of navigation through the dossier via hyperlinks and bookmarks and throughout all sequences. This eases especially the retrieval of submitted documents and gives easy control on existing submissions (KHL)
- Less cumbersome preparation (HvB)
- + Structural organization of data. eCTD provides well established organization of submission data. This allows for more efficient data management; especially in conjunction with an “eCTD aware” EDM system (TED)
- + Dossier evaluation and management improvement via appropriate tools (DrN)

**■ 3.3 eCTD disadvantages**

The second question of the e-mail expert interview was:

*What are the disadvantages of electronic submissions in eCTD format?*

All relevant answers to that question could also be pooled into 8 categories and are sorted by the number of experts giving same or similar answers as follows:

- Stands for nearly the same answer as the category title
- + Stands for additional answers summarized in the category

**A) Implementation/migration and training costs****(5 out of 8 experts)**

- + The need to train everyone who contributes documents to your dossier how to do so properly ... (KHL)
- + Expensive and time consuming implementation project, particular for small/biotech companies, hard to implement (SvH)
- + Significant cost of entry (TED)
- Necessity of retraining of existing staff, or acquiring human resources with new set of skills (TED)
- + Cost of eCTD publishing systems for companies with no prior sub-

mission publishing experience (AnA)

- + Cost of remediating documents and data that are not in submission-ready format (AnA)
- + Investments into new software/hardware (DrN)
- Investment into education of existing employees (DrN)

**B) eCTD standard is not yet sufficient enough (4 out of 8 experts)**

- + The rather stringent eCTD specification do restrict flexibility in the organization of documents in certain cases (granularity aspects) and require a certain submission pattern (e.g. consecutive variations of different types, communication with agencies outside the eCTD, handling of national translations) that does not always fit to the regulatory requirements (KHL)
- + The tendency of some agencies to make their specific interpretation of eCTD specifications a mandatory issue (KHL)
- + The granularity of the current standard is not flexible enough. One should be able to choose different levels of granularity without getting locked in to that level for future revisions (HaM)
- + Still limited harmonization of metadata across various regulatory standards (TED)
- + Lack of consistency of eCTD requirements across the ICH regions (AnA)

**C) Use of bookmarks / hyperlinks and PDF (3 out of 8 experts)**

- + The use of PDF is too restrictive (HaM)
  - PDF files are information blobs and PDF content cannot be managed in an automated way
  - PDF links can easily become broken links
- + Most of the content in eCTD is presented in the PDF format; this limits content description, re-organization and structuring (TED)

- Bookmarking and hyperlinking legacy documents in time and resources (KaS)

**D) One-way communication****(3 out of 8 experts)**

- + The “one-way road character” of the eCTD: The applicant sends a full submission to the agency and gets no xml-backbone back (KHL)
- + The standard does not inherently support reviewer’s comments, annotations and two-way communication (HaM)
- One-way communication (TED)

**E) New processes (negative)****(3 out of 8 experts)**

- + Reviewing and annotating complex documents is still easier on paper (some reviewer print the eCTD and review on paper) (HaM)
- + Redesigning internal systems/processes for eCTD. Steep learning curve (TED)
- Change of already established processes (DrN)

**F) Lack of qualified people****(3 out of 8 experts)**

- Lack of qualified operators of eCTD publishing systems (AnA)
- + Investment into eCTD people (education) or external CRO (DrN)
- + Different skill sets required for preparing an eCTD when compared to a paper submission (KaS)

**G) Additional IT and electronic archival costs (3 out of 8 experts)**

- + The still unsolved problem of long-term archiving of electronic data (KHL)
- + Assuring compliance with regulations pertaining to electronic systems (e.g. 21 CFR 11) (TED)
- + Unknown factor of long-term stability of submission data (lifetime of DVD, CD etc.) (DrN)
- + Cost to establish long-term stability in case of hardware and eSubmission, IT environment is antiquated every 5 years (DrN)

## H) Life cycle and post-approval maintenance (negative)

### (2 out of 8 experts)

+ Difficulties in defining document granularity and metadata that allow transparent life cycle management (HvB)

• The current eCTD standard does not completely support document and application life cycle (HaM)

All answers are summarised in Fig. 1.

### ■ 3.4 Possible reasons for a current eCTD implementation

Another question of the e-mail expert interview was:

*Why do you think some companies have already implemented eCTD submissions?*

The most common answers were:

- Because more and more National Competent Authorities are strongly recommending or mandating eCTD as the electronic-only submission type (KHL, HvB, TED, DrN, KaS) and
- Companies had already started to work with an electronic submission process and had already proven advantages of following old eSubmission Standards (HaM, SvH, TED, AnA, DrN)

Additional answers were that pharmaceutical companies want to show innovative thinking or they are aiming at an early adopter strategy (HaM, DrN) or believe in the above mentioned advantages of eCTD processes (Dif).

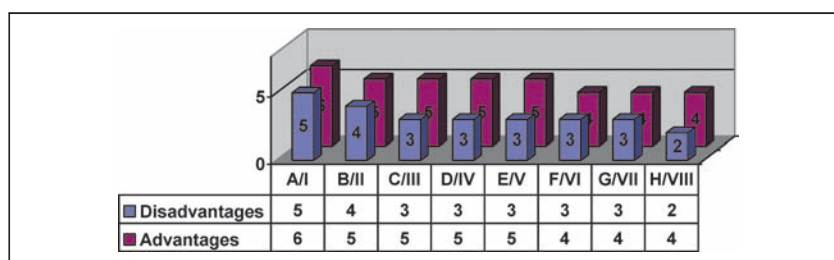
### ■ 3.5 Possible reasons for no eCTD implementation so far

Additionally the experts were asked the following question:

*Why do you think some companies have not yet decided to implement eCTD submissions?*

The most common answers to this question were:

■ Figure 1



#### Summary of answers.

- There are still a lot of agencies where the eCTD submission is not yet mandated or they still require paper (e.g. most of non-ICH countries) for an indefinite period (KHL, HvB, HaM, AnA, DrN)
- You need money before you can save money (HaM, TED, AnA, DrN)
- Resistance of change pattern (SvH, TED, AnA, DrN)
  - “If it ain’t broke don’t fix it” (HaM) or
  - “eCTD is great but we still love paper” (KaS)

Additional answers were the fear of a “refuse to file” because of pure technical issues (AnA) or other above mentioned disadvantages of eCTD processes (Dif).

### 4. Summary and conclusion

Finally it is important to mention:

- Some answers were duplicated or mentioned twice to be able to fill them into two or more categories.
- The category Life Cycle and Post Approval Maintenance exists in both the “advantages” and “disadvantages” list.
- The category New processes also exists in the “advantages” and “disadvantages” list.

- It was possible to group all relevant advantages and disadvantages in each case into 8 categories:
  - But this cannot be seen as equality of disadvantages and advantages.
  - Whether the number of nominations reflects the importance of the pro or the con can only be found through the second part of the social research – the online survey.
- One trend which became obvious already from 3.1 and 3.2 is the advanced consensus of the experts for the advantages than the disadvantages. All eight categories have more nominations than the “disadvantage” categories. This can also be seen in Fig. 1.

An interesting perspective to end this topic is one of Dr. Neurauter’s statements regarding the consistency of an eCTD process: “... the intro of eCTD means introducing a living organism; it also undergoes permanent changes ...”.

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