



## eCTD: Will You Be Ready for 2009?

With the mandatory requirement for eCTD approaching, Shylendra Kumar of Datafarm Inc considers the change from paper CTD to the electronic version, and take a look at what's available to help ensure readiness and eCTD compliance



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Depending on where you operate in the world (especially if you are filing regulatory submissions in the US, EU, Japan or Canada), the eCTD will become a major part of your working life in the very near future, if it isn't already. In Europe (except for the UK and Belgium, who already require either eCTD or another form of electronic submission) there is a commitment that agencies should be ready to accept eCTD submissions with no accompanying requirement for paper by the end of December 2009. In the US eCTDs are already being accepted and will effectively become a requirement from January 2008. In Japan it is optional and in Canada hybrid eCTD submissions (part paper CTD and part eCTD) have been accepted since 30th June 2006, with plans to accept a complete eCTD, although the deadline has not yet been established by Health Canada.

### KEY BENEFITS

The common structure across regions will significantly reduce content preparation time and enable reusability across the regions. The cross-referencing of a single physical document from multiple locations within the submission structure, and across submissions within the application, should eliminate duplication of content submitted to agencies.

For 'usability', the navigation offered by an eCTD will make it easy to find a specific document or piece of information in any application. The 'life cycle management' aspects make it easy to determine the status of a document without reading the content; and with no system dependency, the interoperability of the eCTD will enable easy export and import between systems.

### HOW TO FIND THE RELEVANT SPECIFICATIONS

Relevant eCTD specifications for your individual needs can be found at the ICH website (1), ICH party websites (EMEA, FDA,

MHLW and Health Canada) as well as national agencies websites. The ICH controls overall standards and provides specifications for Modules two through five. Module one contains regional content and specifications provided by regional agencies (FDA, EU agencies, MHLW and Health Canada).

### EARLY ADOPTION: THE PROS, CONS AND CHALLENGES

Thomson's 2005 Lipient Regulatory Affairs Trends Survey (covering US and European pharmaceutical companies), reported that 19 per cent of respondents had already been, or were in the process of migrating, and one-third (32 per cent) planned to migrate to the eCTD within 10 to 18 months.

We're not seeing a 'typical' early adopter of the eCTD; it all depends on the organisation, its involvement in, and commitment to being a front-runner by taking advantage of new agency initiatives.

Generally the tier one organisations tend to adopt first as they have more resources to dedicate to new initiatives, but there are many small and medium-size companies who adopted new technologies, specifically eCTD.

One example is a small pharma company in San Diego, California, that submitted not only its first eCTD, but the first eCTD to be received by EMEA in November 2003. For a company to submit its first submission using a brand new technology is very unusual, but it does prove that early adoption is not just for the 'big boys'.

The advantages of early adoption are persuasive:

- ◆ It gives personnel time to learn, understand and pilot systems before going to production
- ◆ Investment can be minimised with a considered approach
- ◆ It creates time to develop in-house expertise and knowledge
- ◆ It eliminates rush or confusion
- ◆ In the early days, agencies are generally willing to help you learn

And the downsides of late adoption are fairly obvious:

- ◆ Lack of time to develop in-house expertise and knowledge will lead to dependency on external resource
- ◆ Vendors and service providers may perceive a sense of urgency

As always, the early adopters have blazed a trail for the majority by identifying issues and challenges and forcing resolution.

The major practical issue has been the constant change in specifications and guidelines at both ICH and regional levels. This was inevitable in the early stages of eCTD as it was new to both agency and sponsor, and has been compounded by the limited number of companies that have been committed to trying eCTD and identifying the issues. The situation has stabilised and ICH has committed to control the changes and update the guidelines only once in every two years. However, it is important to bear in mind that further changes are inevitable.

Equally challenging has been the need to change behaviour. The natural resistance to change is often

institutionalised in companies and makes taking that final decision to 'jump' very difficult; companies typically find ways to avoid it and delay making that decision until forced to do so.

Knowledge plays an important role. Lack of understanding about CTD, eCTD, what it is and what it does, makes it very difficult to appreciate the advantages. Some people are purely intimidated by the new technology and buzz words such as XML, XSL, DTD, and so on. The companies that have followed a 'wait and see' policy have, to some extent, benefited – they simply haven't had to deal with the early implementation issues.

However, what is clear is that every company presents new issues as every application has its own individual level of complexity, so the challenges of implementing eCTD cannot be completely avoided, and with 2009 fast approaching it is time to 'bite the bullet'.

### HOW TO MAKE THE CHANGE?

Simply put, the stages involved in adapting to eCTD are exposure, education, training and buy-in. First, try to understand what eCTD is and the advantages and disadvantages of eCTD to your business. Secondly, educate the people who are involved in the submissions content creation process about eCTD and build awareness within the organisation – this process helps to avoid roadblocks later on when you implement. Developing 'buy-in' and an understanding of the organisational areas of impact from various viewpoints across management, disciplines and functional levels is also key to success.

Thirdly, take a smaller submission or existing submission and create a 'training' eCTD. This submission doesn't even have to be a real one. Send it to a relevant agency as a 'test' submission. Ask your users who are involved in the review process to look at it and compare it to your existing paper or other electronic format. For non-eCTD submissions, when the agency sends a query, a significant amount of time is used up attempting to locate the folder and specific page in order to respond to queries from the agency. With eCTD, this information will be at their fingertips.



Finally, go into production. Some companies switch over all their new NDAs/MAAs to eCTD format. Some start by using eCTD for all their new INDs, and some switch to an eCTD format for all in-review INDs previously submitted in paper or other electronic formats. You should consider this switching option carefully and only after discussions with the agency. Similarly if you have an approved MAA at the agency and are now filing a variation, you could, following discussions with relevant agency and approval, switch over to eCTD.

## IMPLICATIONS FOR SYSTEMS, PROCEDURES AND PEOPLE

eCTD is all about standards and structure. Technology plays an important role, but we do not believe that technology is a most challenging factor in this initiative. Knowledge and understanding of the requirements are critical factors since eCTD is based on CTD structure, first you have to make sure that your authoring environment understands and prepares the documents following the CTD standards, particularly with regards to the granularity of the documents (see ICH M4 Organisation Document : Granularity Appendix).

The review (including QA/QC) community needs to understand the content and technical requirements, and pay close attention to those details. The technical team should understand the requirements and provide necessary infrastructure (tools and systems) to the authoring and reviewing community.

Some companies try unsuccessfully to create electronic submissions at the end of the process, collecting all the documents from various sources and publishing them within regulatory operations group. This may work for paper and other types of e-submissions, but it will not work for eCTD unless the authoring environment is updated to CTD standards. If the documents are created based on a clear understanding of the requirements, then the publishing and compilation task will be straightforward and effortless.

## ENSURING COMPLIANCE

Following all current ICH specifications and regional guidance will guarantee eCTD compliance. This level of compliance requires collaboration both from a system or software perspective, as well as internal processes, such as authoring, publishing and quality checking final output.

Technology may well be essential, but it cannot be expected to fulfil all your eCTD needs. As mentioned earlier, if your documents are not created according to CTD standards, then no software application will be able to produce a compliant eCTD.

For example, if the information about the quality expert is placed under section 1.7.2 Market Exclusivity, the software application is not going to complain; it is technically valid to add a document under a section. We do not eliminate the need

for regulatory expertise, content knowledge and the decision-making process to ensure that information about the quality expert is added under section 1.4.1 Quality. The software merely assists in the process by displaying the prescribed structure and providing an easy-to-use interface. Software will also help assure the user that technical requirements are met in the prepared submission. So, at the end of the day it is a combination of people, knowledge and software that produces a compliant eCTD.

## CROSS-BORDER AND MULTI-AGENCY SUBMISSIONS

Unfortunately, there are some challenges involved in cross-border and multi-agency submissions, and in some regions it is more complicated than others. These challenges and complications seemingly result from moving away from the common format, and are completely attributable to lack of real-time experience.

We have worked with many sponsor organisations on submissions to multiple regions for the same application where over 70-80 per cent of the content was re-used across all applications. This was possible only because of eCTD. Initially, we did not experience any issues, but later on in the lifecycle we noticed issues and presented them to ICH and regional authorities. Similar experience and feedback was submitted by many other sponsor organisations who were early adaptors.

Some of these challenges have been taken care of through updated guidelines, some are yet to be resolved, and agencies would like to gain more experience before updating guidelines yet again.

It is imperative to talk to agency and reviewers prior to submitting your first cross-border eCTD. Also, it is very important – especially if you are going to submit an application to multiple regions – to have all regional parties within your organisation involved in the discussions and planning from day one. Consider regional requirements and prepare your documents accordingly.

## HOW LONG WILL ALL THIS TAKE?

The time taken from starting the process (gathering requirements) to being completely changed over to eCTD varies from company to company. The variation is driven by many factors within the company: knowledge, resources, infrastructure, priorities, and so on.

Some companies have gone into production within a month of the day they started the discussion, whilst others have taken over a year to complete the process.

Typically, it is possible to be up and running in production mode from between one to 12 months. One month is more likely for a small organisation and six to 12 months for a very large pharma

with multiple country deployment. These timings include negotiations, installation, validation and end user training.

## HOW TO IDENTIFY THE APPROPRIATE ECTD SOLUTION?

Make sure your chosen solutions provider has:

- ◆ Detailed knowledge of eCTD
- ◆ Knowledge and an understanding of your business and day to day operations related to regulatory submissions
- ◆ Been a provider of regulatory submissions solutions in the past
- ◆ A good track record as a subject matter solutions provider

And ensure that the solution:

- ◆ Can produce eCTDs that are compliant with current ICH and regional specifications and guidelines
- ◆ Is capable of supporting multiple regions and versions
- ◆ Is not brand new and that it has gone through several iterations
- ◆ Is currently used by more than one customer and/or countries
- ◆ Is scalable and reliable (no software is 100 per cent bullet-proof)
- ◆ Will meet your immediate business needs and capable/flexible of handling future needs

Choose your provider carefully. Many technology companies claim that they have a solution, but have little or no industry experience. As mentioned earlier, it is not just the technology that is critical, it is the combination of knowledge, experience and technology that delivers a good solution to your needs. Also, you are partnering with the provider and not just purchasing a solution from them; the collaboration is a never-ending process and not just a one-time deal.

## KEY PRODUCTS AND SERVICES

In terms of products, look for ICH and Regional Agency compliant application(s) to create and view eCTD submissions. The system should have the capability to verify (validate) submissions following ICH and regional criteria list and have required PDF publishing capabilities. Optionally, the system should have the capability to produce print ready paper volumes.

For services, providers should be driven by regulatory and technical expertise. That is, look for a supplier with a deep understanding of what eCTD is all about and the ability to effectively impart this knowledge to all levels within your organisation. Approaching the projects as a collaborative effort between client and provider, and understanding the immediate corporate environment, is vital to the success of any service engagement, as is the ability to execute effective project management, including risk assessment, methodical issue

resolution and documentation. Finally, your chosen provider should understand the eCTD deliverables and have the ability to deliver on time, incorporating project closure to ensure customer satisfaction.

## WHERE'S IT GOING AFTER eCTD?

As stated earlier, this is a never ending process. The technology and business requirements force agencies to consider changes in systems, guidelines, process, and so on, to make drug development more efficient and cost effective.

For example, the FDA is concentrating on a new standard called regulatory product submission (RPS) in collaboration with HL7. The reason for this new initiative from the FDA is to have a single standard for all types of submission they regulate. The eCTD is focused only on human drugs and does not cover devices, veterinary, agriculture and blood-related submissions. The goals of RPS are to have one standard for any type of submission.

You may ask, "If eCTD is going away, why am I wasting my time to implement it?" Remember, it took over seven years for the FDA to implement e-submission (eNDA/eBLA) standards. The e-submissions standard, which started in January 1999, will now be replaced with eCTD in January 2008. The e-submissions to eCTD transition took over six years. With development of the RPS, is it obvious that it will take at least five to seven years. In the meantime, you have to comply with the current standard which is eCTD.

In Europe, it is different. EMEA and EU countries are concentrating on moving to electronic, as even today the required submission format is paper (with the exception of UK, Belgium and the Netherlands). They are currently not actively involved in RPS initiative. However, it is likely that further major development of the ICH eCTD specification will be undertaken in conjunction with HL7 as ICH has recently made a decision to progress development of standards in conjunction with standards development organisations such as ISO and HL7.

From a sponsor's point of view, EU member countries have undertaken the commitment to be ready to accept eCTD submissions with no accompanying requirement for paper by December 2009.

Even if new standards are introduced, it will probably take at least three to six years for those standards to replace eCTD. So, eCTD is here, and we believe it will be there for at least four to five years, or maybe even more. ◆

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## Reference

1. ICH website, [www.estr.org](http://www.estr.org)