

Easing Electronic Migration in the EU

The European Union deadline for manufacturers to use the electronic Common Technical Document when submitting drug applications filed via the centralised procedure has now passed. *Kate Wilber* discusses best practices for e-submissions management.

The first day of 2010 marked the European Union deadline mandating that companies submit electronically all drug applications that are to be reviewed via the centralised procedure.

As of 1 January, the European Medicines Agency has required that the submissions are made using the electronic Common Technical Document. Paper submissions are still legally acceptable, but these are strongly discouraged. There are considerable gains to be made from changing to the eCTD format, particularly in the longer-term with regards to maintaining and amending product licences. Firms of all sizes should, therefore, step up their efforts to automate their document publishing and life-cycle management activities.

Many of the larger companies have already made the transition from paper to electronic submissions; in the US, the Food and Drug Administration's Center for Drug Evaluation and Research mandated the use of eCTD for electronic submissions two years ago. The good news for mid-sized and small organisations that have been slower to make the move to an electronic environment is that they can now benefit from the lessons learnt by their pioneering, larger counterparts.

Best foot forward

A company's attitude towards eCTD adoption is of the utmost importance. Firms that have seen the most positive impact of eCTD implementation to date have been those that have embraced electronic automation as a means of streamlining, and adding value to, internal processes by raising the overall quality, efficiency and timeliness of their regulatory submissions activities.

Having reasonable expectations is also vital. While eCTD promises to transform document authoring as well as submission compilation, review and life-cycle management, the benefits will not be felt overnight. It will take time to train staff and to get the initial eCTD right. At first, the long-term process gains may seem to be outweighed by start-up pains, including the inevitable learning curve.

Getting it right

Pharmaceutical companies that rushed their first eCTD without having taken the time to determine their internal processes and, more specifically, their eCTD metadata standards, have come to regret their haste when faced with the need to make onerous amendments throughout the life-cycle of their product.

The eCTD requires consistency from one sequence to the next; Module 3 of the five eCTD modules, which deals with quality, is one section where decisions on metadata must be made carefully, as this structure will continue to

evolve throughout post-marketing activities.

Sufficient attention must be paid to document structure and file-naming so that hefty submission documents, running to thousands of pages, can be broken down into distinct, easily searchable sections. This approach to document granularity will pay dividends later on, enabling revisions and updates to be submitted and processed without the need to re-send documentation in its entirety. One of the primary advantages of eCTD is its scope for eliminating redundancy from the authoring and submission processes by allowing applicants to submit only new or changed information. At the regulatory authority, the assessor is able to clearly view any individual submission as well as the full submission history in a cumulative viewer. This saves time for both applicants and assessors, and the review can focus on updated information only.

Reducing reliance on paper will, in due course, have a positive impact on internal administrative workloads. Yet electronic submissions, particularly those based on the now preferred eCTD standard, introduce their own house-keeping demands, as submission managers now need to consider the resource required to apply bookmarks and hyperlinks, allowing for navigation through the application.

Regulatory authorities discourage the over-use of hyperlinking as a means of taking the reviewer straight to the required section of documentation; this is because the consistent, formal structure of the CTD and the way this structure is consistently presented in the eCTD viewing tools helps the assessor significantly. It is also important to remember that every link that has been introduced will need to be checked for quality-control before publication, which could prove highly time-consuming. Each link will have to be validated by the regulatory authority too.

Although it is not compulsory in the EU, companies are actively encouraged to submit a "baseline eCTD" when the eCTD format is initiated in the middle of a product's life-cycle. There can be significant effort involved in re-formatting already approved documentation for the baseline submission and applicants should carefully assess how to approach this and ensure sufficient time is allocated for this work. The baseline eCTD gives both the applicant and the health authority a starting point for future life-cycle operations, maximising the benefit of the eCTD.

Assigning roles

Pharmaceutical companies making the transition to electronic submission will need to train or employ eCTD experts, assuming they have not decided to outsource their submissions activities (which is a real and practical

option for smaller enterprises). The metadata management and quality control processes are vital: understanding the impact of these throughout a product's life-cycle will require clear communication between the firm's regulatory affairs and operations teams.

Adequate and appropriate training will be required for all staff that provides input into the eCTD. Training should be tailored to the users' individual needs – for example, non-clinical authoring groups will typically be least involved with eCTD matters, while those on the manufacturing/quality side will have to deal with significant and regular changes to documentation and, therefore, extensive eCTD life-cycle and metadata management. Contract resources, such as clinical research organisations and other groups providing content for the eCTD must also be aware of the drug firm's electronic document delivery standards.

Regulatory affairs employees will require significant training to ensure that they fully understand any changed processes. The company as a whole will need to be brought up to speed on how to review what has been submitted via the eCTD. A significant benefit of eCTD submissions is that they facilitate a complete, holistic view of the entire submissions process, with full traceability of what was sent, when, and with what resulting actions.

Multiple regions, one strategy

An eCTD strategy can and should encompass other, broader electronic and paper submission requirements as well. If a company is submitting licence applications across more than one market, it makes sense to produce a common core dossier, allowing for maximum content re-use wherever practical and possible, in accordance with local regulatory guidelines. The format of the eCTD naturally lends itself towards information re-use in eCTD markets and it streamlines the steps needed to re-purpose the content in non-ICH regions.

In Europe, mutual recognition, decentralised and national submissions are subject to the discrete requirements of each health authority in the different member states, which makes managing eCTDs in these procedures more challenging. Currently, each country in the EU varies with regards to its timelines and demands relating to eCTD adoption. The Heads of Medicines Agencies website

at www.hma.eu/277.html provides information on each country's specific requirements, though these standards are being changed at a rapid rate in many countries and each health authority's website should be consulted. The HMA website also details the ability of various national competent authorities to accept electronic-only applications. Even those countries that accept electronic submissions may still require some paper. Companies would be wise to define a broad strategy that allows for these differences. Equally, when seeking external help, it would be prudent for companies to look for a consultant or technology services partner that has experience in providing advice on managing the submissions process across more than one region, so that they can ensure the best strategy and solutions are used.

However, companies must not lose sight of the fact that the biggest challenges involved in eCTD adoption are process-based – there is a call for rigour in the way that documents are authored, tracked and managed. As noted above, appropriate granularity, well-formatted sections and a consistent authoring style are essential, enabling and encouraging the maximum level of automation, and saving a lot of time – and reducing risk – in the long run.

Seizing the moment

The broader benefits of migrating to eCTD are well-documented. Companies that are now starting to adopt eCTD can benefit from the lessons learnt by the firms that have already embraced the technology, thereby bypassing many teething problems and deriving faster benefits.

Waiting is no longer an option. While paper has not yet been entirely consigned to the recycling bin, firms that persist in printing before sending their submissions may now find themselves out of sync with regulatory authority standards, whose purpose is to ease and accelerate the review process.

Rather than ignore the need for eCTD adoption, or worry about getting it wrong, it would be far better for companies to actively engage in discussions with the relevant regulatory authorities during this transition period. It is likely that the authorities will be sympathetic to the challenges involved since they too are facing substantial change as they migrate their own internal processes to eCTD.

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