

The evolution of the eCTD

Tim Felgate describes the sometimes painful transition from paper to electronic submission dossiers

As recently as the 1940s, submissions to support the marketing of medicines were small single-volume dossiers containing fewer than 100 pages of data, most of which was manufacturing information. Since then a number of serious adverse reactions associated with the use of medicines have led to an extensive review of the regulatory framework for medicines. The most notable example of this was the tragedy associated with the use of thalidomide during pregnancy. Following this, most developed countries around the world introduced a raft of legislation that requires an extensive review of the safety, quality and efficacy of a medicine before it can be granted approval for placing on the market.

This has resulted in a sudden and dramatic increase in the volume of data that needs to be generated and submitted to the regulatory authorities. Whereas, at the end of the 1950s a typical dossier for a new medicine would comprise two volumes of data at the most, just 10 years later this had increased to nearly 200 volumes. With this increase in volume of data came a need to build tables of contents and cross-referencing to facilitate the navigation of the dossier. The remainder of the millennium saw dossiers increase further in complexity and size, and this has been accelerated by the harmonisation that has taken place both within regions, such as the European Union, and across regions, driven by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The extent and complexity of the data required today has meant that the development programme for new drugs has become a lengthy and expensive process, involving substantial preclinical and clinical studies.

For many years, submissions have been prepared in accordance with the specific national requirements of the countries where the medicinal products are to be marketed. Increasing co-operation among the regulatory authorities, spurred on by initiatives such as ICH, have looked at ways of reducing time-consuming reworking of data for each region and focused on producing a harmonised set of requirements, both for the data needed and for the format in which it is presented. It is the harmonisation of the presentation of data that has led to the definition of the Common Technical Document (CTD), which was first agreed in 2000. It is important to understand that the CTD only defines the format and

structure of the data dossier for submission and does not define the data content that is required. The data required are defined by the various legislation and guidelines in each country. Many of these guidelines have also been harmonised due to the efforts of ICH.

The CTD organises the data into modules at the highest level, through nodes to individual documents at the detailed level. The modules that comprise the CTD are Modules 2–5 of the submission and contain the scientific data and summaries. Module 1 of any submission is not part of the CTD and contains region-specific administrative information. The organisation of the data into modules and nodes is referred to as the ‘granularity’ of the submission and is tightly defined in published guidelines.

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However, it is clear in what direction these changes are moving.

Migration from paper to e-dossiers

The last two decades of the previous millennium saw an explosive increase in the accessibility of information technology. This has been greatly accelerated by the emergence of personal computers together with their rapid decrease in cost. The increase in connectivity afforded by the advent of the Internet has also made a major impact. Together these have provided valuable tools to assist in the process of assembling submission dossiers, drawing together data from multiple authors and locations almost instantly. Prior to the information technology revolution, dossiers were prepared, often in one location by a dedicated registration department, using such tools of the trade as typewriters, scissors, glue and photocopiers. The arrival of the newer technologies has greatly facilitated the process

by allowing multiple authors to collaborate on a submission, across different geographic locations, allowing multiple drafts and their reviews by key experts. This has done much to improve the quality of submissions and reduce the time taken to prepare them. For many years, however, paper has still been the principal output for delivery to the regulatory authorities.

The submission of large amounts of data to regulatory authorities has created problems for both the pharmaceutical industry and the regulatory authorities. Large paper-based dossiers are unwieldy and place a heavy demand on physical space for their delivery and storage. The advantages of the new technologies soon became apparent as a means for transmitting and storing the data, and in 1994 the Multiagency Electronic Regulatory Submission (MERS) project was initiated among the regulatory authorities in the USA, Canada, Netherlands, Sweden and Australia.

This project placed an emphasis on how best to manage the scientific data generated in a structured way and transmit it to the regulatory authorities in the most efficient manner. Following the agreement of the CTD at ICH, the focus shifted from the MERS project to developing Electronic Standards for the Transfer of Regulatory Information (ESTRI), which has given rise to the electronic CTD (eCTD). The eCTD defines a structured compilation of electronic documents arranged in specific folders and referenced from a hierarchical data file in XML format, often referred to as the ‘XML backbone’ of the dossier. The documents are presented in Portable Document Format (PDF) to reduce the dependence on proprietary document formats. The eCTD is usually assembled using specialist software and can be read with a standard internet browser and PDF viewer.

The eCTD is now the expected format for submissions in the US as well as a number of European national competent authorities and, from July 2009, the EMEA. Each of the 31 regulatory competent authorities in Europe is at different stages of readiness to accept eCTD submissions. To permit a quicker transition to electronic submissions, a further standard was developed among the European authorities, known as the ‘non-eCTD electronic submission’ (NeeS). This is essentially the same collection of PDF documents found in the eCTD, but with a PDF table of contents instead of the XML backbone, and is seen as a stepping-stone towards the eCTD.

As authorities are undergoing the transition from paper to the eCTD, we are currently faced with multiple requirements reflecting the various levels of readiness. A global submission across the ICH regions demands various combinations of paper-only, eCTD, NeeS and mixed applications with some parts provided as paper and some parts as electronic documents.

This, together with the various regional and national data requirements, has resulted in a highly complex submission environment. This should eventually become simpler, as more authorities adopt the new standards and further efforts are made to harmonise the data required.

So far there has been a lack of consistency among the authorities, both between and within the major regions. Ambitious targets have been set and have then had to be modified in response to various pressures. However, it is clear in what direction these changes are moving. What remains uncertain is the exact timing to which some authorities are working.

Submission life cycle

Following the initial regulatory submission for a new medicine, the registration file is continually updated in the light of new safety, quality and efficacy data and in order to accommodate commercially necessary changes to the manufacture.

These variations to the initial marketing applications form discrete submissions to the regulatory agencies. Each of these submissions adds, deletes or changes data in the registration file and becomes an integral part of the life cycle of the registration. At any point in time, the registered information is a function of the original submission and all of the subsequent changes to it. With paper-based submissions, determining the current registered information is a complex process involving an exhaustive trawl of the original registration submission and each subsequent variation to it.

The demand this places on resources at the regulatory authority and the applicant is significant. To this end, both regulators and applicants alike often maintain a current status file in addition to the individual submissions that underpin it. Sometimes information can be misplaced, leading to uncertainty about what is actually registered. This possibility is greatly increased when products are transferred to other companies, and documentation can sometimes be incomplete.

The development of the eCTD standard has put in place an integral life cycle management,



with each submission being designated as a discrete 'sequence', identified numerically. Thus the initial submission is assigned a sequence number 0000 and the number is incremented with each subsequent change. As each sequence identifies clearly what has been added, changed or deleted, it is relatively simple to use a software viewer that automatically rolls up all the changes to indicate the current registered information for each element in the registration file, as well as provide a detailed history of changes made. It is expected that this will lead to significant decreases in the time taken to assemble variations by the applicant and the time taken for their assessment by the regulatory authorities. These benefits have still to be seen, as they have been largely offset by the need for assessor training and familiarity with the new systems.

Changing business practices

A couple of decades ago, submissions would be prepared for output on paper by the local offices of the applicant, with varying degrees of support from the headquarters. These would use data from a variety of sources, including different manufacturing sites and study centres. Data would often have to be transcribed to meet the local submission requirements. Today, we see increasing collaboration among departments, with multiple authors contributing their parts to the submission. This has been further enhanced by the introduction of electronic document management systems (eDMS) in some companies, which have increased the speed and reliability of document review by the use of defined workflows that transcend departmental and geographic boundaries. The use of eDMS also facilitates compliance with certain regulatory requirement for document audit trails, such as those set out in 21 CFR Part 11 (for the US) and Eudralex Volume 4 Annex 11 (for the EU).

The move to an increasingly structured approach to handling and presenting data requires new skills and different working practices for everyone involved. For example, many people have taken to using word-processing software as if it were a typewriter on steroids. This takes no account of how the document is structured and its internal hierarchy. Documents from poorly trained authors require substantial reworking to ensure that the internal structures are incorporated. For example, headings need to be defined as such, and not just reformatted normal text. Properly defined headings can then be read and understood by the software used to generate the structure of the eCTD. Thus, the author's originally intended structure can be automatically

mapped through to the final submission. It is essential that sufficient resource is allocated to training all authors so resources are not wasted in reworking documents to comply with the structure of the eCTD. Templates are often used to improve consistency; however, their value is largely negated if adequate training is not provided.

With the changes to business processes, roles need to be re-examined to ensure the overall processes and those responsible for operating them are optimised to align with company objectives. For example, the division of responsibilities between company headquarters and the local affiliate offices needs to be considered with a view to finding the most efficient ways of working for the company concerned. The roles that have worked historically for paper-based submissions are likely to be very different from those required to support eCTD submissions. We are seeing an increasing specialisation, with regulatory affairs

departments taking responsibility for planning regulatory strategies, and regulatory operations departments taking responsibility for the preparation and management of submissions.

Future trends

The eCTD presents data as 'leaf' documents (usually in PDF), where the smallest discrete data object is the leaf itself. Various initiatives, including the MERS project, HL7, PIM and the use of SmPC fragments by some authorities, are focusing on breaking down the structure and granularity of the eCTD to a level much lower than that currently defined by the leaf documents. Also, the emphasis is moving away from presenting data as PDF (which can be considered to be an electronic representation of the familiar paper page) to using more structured data formats such as XML to handle the raw data as well as labelling information in a more reusable manner. In this way a particular data element

can be represented in multiple formats and places in a totally consistent way. Any company implementing new systems and processes needs to take these new trends into account in designing them. A paradigm shift is also required in how we think about the data.

The data can no longer be thought of as linear documents with pages, a beginning and an end. The data now needs to be considered as a hierarchy of data fragments that can be presented in different ways as defined for each particular purpose.

It is especially important, as the regulatory framework is rapidly evolving, to ensure that the data are in a reusable format that can be represented in whatever format is required at the time.

Tim Felgate is a senior member of TOPRA and the managing director of Applied Regulatory Consulting. He can be contacted at: tim@appliedregulatory.com

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Key developments

In response to a number of serious adverse reactions in the 1960s, legislation was introduced that requires an extensive review of the safety, quality and efficacy of a medicine before it can be placed on the market.

As a result, submission dossiers increased in complexity and size.

Since the 1980s, there has been an explosive increase in the accessibility of information technology.

Large paper-based dossiers are unwieldy, and the new technologies offered advantages as a means of transmitting and storing the data.

In 1994 the Multiagency Electronic Regulatory Submission (MERS) project was initiated.

Increasing co-operation among the regulatory authorities, spurred on by initiatives such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), led to an increased focus on producing a harmonised set of data requirements.

In 2000, the Common Technical Document (CTD) was agreed, which defines the format and structure of the data dossier.

Based on this, the ICH developed the eCTD. This is now the expected format for submissions in the US and, from July 2009, the EMEA.



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T: +44 (0)1243 772030
 E: subscriptions@wiley.com
 W: www.inpharm.com

