



Electronic submissions: Past, present and future

By Stan van Belkum

The business case

Some ten to fifteen years ago, two trends became visible in the pharmaceutical regulatory world. First, the ever expanding rules, regulations, directives, laws, guidelines, etc. led to an enormous growth in the size of a regulatory dossier for a new human medicinal product. Dossiers for new chemical entities of more than 100,000 pages became common practice rather than the exception, and those for products derived from or with biotechnology were even larger. Secondly, the pharmaceutical industry was undergoing rapid consolidation, with mergers and acquisitions leading to the creation of truly global conglomerates. To quote just one of many examples: Glaxo acquired first the Wellcome Foundation, and soon thereafter SmithKline Beecham, forming the pharmaceutical giant GSK.

As a result of such developments, managing large numbers of enormous pharmaceutical dossiers globally became an almost impossible task. At the same time, the computer and computerized systems—databases, but also document management and tracking systems—found their way into day-to-day office life. So the two partners in regulation—industry and authorities—focussed their hope on the computer and electronic systems. Electronic regulatory submission became the buzzword or magical term that was going to solve many problems.

From a regulatory perspective, the business case was not only the review but also the facilitation of logistic and administrative procedures (no more endless corridors with pallets of paper), enhancement of agency transparency (both regulatory and financial), knowledge management, and last but not least the dissemination of information on medicinal products to healthcare professionals, patients and the general public. With regard to review, the main problem an electronic submission was intended to solve was life-cycle management. With a paper archive of regulatory information, it is obviously difficult to find the most up-to-date information. Finding the currently valid Summary of Product Characteristics or the most recently approved specifications of the finished product is a time-consuming and problematic task in the paper world. With an electronic dossier, this information should be just a click away. Another critical review issue is navigation within and between files: a clear benefit of electronic files is the ability to (hyper)link information. However, electronic dossiers with poor navigation (e.g. scanned pages only, with no bookmarking or hyperlinks) are worse than a paper-based file!

For the pharmaceutical companies, the main aspect of interest is to keep their business manageable at the global level while at the same time gaining time in the approval process for their pharmaceutical products.

Early initiatives

In the late 1980s and early 1990s, several national and international initiatives tried to set a standard for electronic submission of regulatory information. Examples are:

- MANSEV (Market Authorization by Network Submission and Evaluation): an initiative of the European Commission and the national agencies of the UK and France
- DAMOS (Drug Application Methodology with Optical Storage): an initiative of the German authority and German pharmaceutical companies
- MERS (Multi-agency Electronic Regulatory Submissions): an international working group with members from the FDA, Health Canada and the national agencies of Sweden and the Netherlands
- SEDAMM (Soumission Electronique des Dossiers d'Authorisation de Mise sur le Marche): a French initiative
- IRF (International Reviewer Forum): a forum for actual users of electronic submissions

Despite their good intentions, none of these groups succeeded in developing a real solution. Each initiative favoured a specific standard, ranging from all PDF-based submissions, to TIFF-based solutions, to HTML and SGML structured information. As a consequence, regulatory agencies were confronted with many different systems for the submission of electronic regulatory information. Each of the systems had a learning curve for the reviewers, and sometimes even very specific software and hardware had to be used. Although some experience was gained, the anticipated benefits were not met, and basically the situation was more complex than in the old days with only paper submissions.

The breakthrough finally came about with the International Conference on Harmonisation (ICH). Within ICH, the Common Technical Document (CTD) was under development. The goal of the CTD was to harmonise the table of contents for pharmaceutical dossiers in the three regions involved: the US, Japan and Europe. Given the developments mentioned above and the problems encountered with electronic submissions, it seemed a logical idea to

Electronic submissions

charge one of the ICH Expert Working Groups, the M2 EWG, with the development of an exact electronic version of the CTD. This result would be a globally acceptable standard for the submission of electronic regulatory information. The work started at the end of the 1990s and led in September 2002 to the first international standard, the electronic CTD (eCTD) specification version 3.0.

The eCTD specification

The eCTD specification version 3.0 is a detailed description of the eCTD. However, it should be noted that the eCTD is an exchange standard. It only describes how regulatory information is transferred from a pharmaceutical company to a regulatory agency. It does not describe how an eCTD should be generated nor how an eCTD can be used in a regulatory agency. The heart of the specification is the so-called Document Type Definition (DTD) describing the table of contents of the CTD and adding meta—data to the files contained in the submissions in XML, eXtensible Mark-up Language. XML is considered the next—generation Internet meta-language, and its choice has been the subject of long and heated debate in the ICH M2 EWG.

An eCTD has four basic components:

- A directory structure which mainly contains PDF documents; the names of both the directories and the files are based on a standardized nomenclature.
- Two XML files: a so-called XML backbone for Modules 2 to 5 of the CTD and a regional XML backbone for Module 1
- An MD5 checksum¹ for the total submission
- A stylesheet allowing the eCTD to be read in a web browser

Details of the eCTD specification can be found on <http://estri.ich.org/> and <http://esubmission.emea.eu.int/tiges/index.html>.

Current status of implementation of the eCTD in the EU

After the development of the eCTD specification, according to normal ICH working procedures, the standard had to be implemented in the three regions. This procedure is already quite complex in the EU for ordinary ICH guidelines, but for a technical standard like the eCTD, this was even more complicated. The specification not only had to pass the CHMP; it also had to be supplemented by the regional standard for the Module 1 and explained to the Member States. The refusal of the FDA to start implementation was a further complicating factor. The FDA needed additional pieces of information and re-started the discussion within ICH on the eCTD specification. This caused a considerable delay in the EU.

The main organisational structure to do the implementation work was fortunately already in place. Information and Communication Technology (ICT) projects at the European level were run through a Telematics Steering Committee (TSC) chaired by the Commission, controlled through a Telematics Management Committee and performed by so-called Telematics Implementation Groups (TIGs) in which all Member States are represented. In this case, the TIG on electronic submissions (TIGes) was responsible for the work. The TIGes established the necessary working relations with important partners that had to be part of this implementation. The Notice to Applicants (NtA) Group, Quality Review of Documents (QRD) group at the EMEA and several industry associations were and are part of this network.

The results of this cooperation between the different organisations over the last couple of years are quite impressive:

- The EU Module 1 Specification
- Electronic Application Form Specification
- Electronic Variation Application Form
- Guidelines on the eCTD and paper eCTD
- Question and Answer document
- Questionnaires on statistics on the eCTD

Although the implementation of the eCTD specification in the EU can be considered relatively successful, several important lessons have been learned:

Lesson 1: The development of a standard is one thing, but the actual software implementation is another.

At the time the eCTD specification version 3.0 was finalised, no software was available to either generate an eCTD or accept an eCTD. Basically the XML file had to be written by hand in XML editors and could only be read by simple stylesheets. This led to a slow acceptance by industry and regulators. The reason for the delay between finalisation of the specification and the development of dedicated software was the fact that vendors were involved only at a very late stage in the development. Now, however, there is a large choice of eCTD software² available. In general, the software provides the following functionality:

- Use of templates
- Drag and drop of files in a predefined directory structure
- Automated generation of the relevant XML files and MD5 checksums
- Validation of the output XML files
- Viewing of an eCTD, i.e. tables of contents per submission, cumulative views of the table of contents, document information, document pane, etc.

With the variety of software tools, a new problem arose. eCTDs generated with tool A could not be viewed with tool

¹ An MD5 checksum is a hashcode of 32 characters and numbers allowing integrity checks if the eCTD is copied from the hard media to a different location. Not only the complete submission has a checksum, but also all the individual files have checksums that are part of the meta-data included in the XML backbone.

² Software is available from ISI, Lorenz, Datafarm, IBM, Lipient, IAGB, Sendar-Menlha, GlobalSubmit, etc.: check their websites for more information.

>>> Electronic submissions

B and vice versa. There was clearly a difference in interpretation of the specification. This led to the development of a list of validation criteria by the ICH M2 EWG that should solve future validation problems and stimulate the development of interoperable tools.

Lesson 2: Setting up the relevant working relations has taken too much time

The eCTD is an area where the interests of regulators and industry might have more in common than in other areas. Too much time has been lost by the regulators trying to solve all the implementation problems on their own, while many of the solutions were within the jurisdiction of the pharmaceutical industry or software vendors. Vendors in particular need to be involved at an early stage in the development of an electronic standard.

Lesson 3: Setting a clear business driver is critical

Although around the year 2005 all the basic components for successful introduction of the eCTD were available—specifications, software, cooperation—the eCTD did not fly. An overview of the number of eCTDs filed in the EU by the end of 2005 can be found in Table 1.

Table 1. Number of eCTDs filed in the EU by the end of 2005

Organisation	Number of eCTDs	Maximum life-cycles	Remarks
EMEA	46	Around 50	About 10% of the total applications to the EMEA are in eCTD format
All Member States	115	Around 50	Range per MS from 0 to 79 eCTDs
The Netherlands:			
– National	32	Around 40	In 2006, already more than 50 eCTD submissions have been made to the Dutch agency.
– MRP CMS	1		
– CP	46	Around 50	

CMS=Concerned Member State, CP=Centralised Procedure, MRP=Mutual Recognition Procedure, MS=Member State

From this table and the total number of submissions in the EU, the conclusion can be drawn that less than 1% of all submissions are in eCTD format. An initial analysis of this fact provided the following possible causes:

- Underestimation of the technological impact
- Underestimation of the business impact
- Unclear or weak business case for pharmaceutical companies
- No strong regulatory driver (i.e. providing regulators with eCTDs is not mandatory)

In particular the lack of a regulatory driver was often heard as an excuse from companies for not starting the internal development of streamlining business processing to focus on production of an eCTD. Clarity on the business driver was given by the Heads of Medicines Agencies (HMAs) in 2005. Their statement contained the following important points:

- The HMAs endorsed a target date of end of 2009 for implementation of eCTD submission without paper by all National Competent Authorities.

- The European Regulatory Network will, by the end of 2009, have the infrastructure and the processes in place to handle electronic submissions of eCTD for marketing authorisation applications without paper and to be able to make the best use of them.

At the same time, the HMAs made it very clear that this doesn't mean that eCTD submission would be mandatory in all states by that date. However, authorities and industry should not wait until this date to implement the eCTD. This approach allowed Member States and the EMEA to move to eCTD-only submissions at different speeds. There is some evidence of rapid adoption of the eCTD-only situation:

- In Belgium, electronic submission is mandatory with a high preference for the eCTD.
- The EMEA has set a target date of December 2006 for eCTD-only submissions.
- In the Netherlands, electronic submission will become mandatory at the end of 2006, and eCTD-only submission is targeted for 2007.
- Several other authorities are very active in this area (UK, Portugal and Ireland).

Future eCTD developments

Two developments are considered critical for the future success of the eCTD: further improvement and refinement of the current specification and continuous harmonised implementation of the standard.

eCTD specification beyond 2007

For the following reasons, the ICH process to develop message standards for the pharmaceutical world is currently being reviewed:

- More work is being brought to the ICH M2 EWG by other working groups (e.g. in the area of pharmacovigilance), and there are insufficient skills and manpower to keep up with the expectations.
- There are limitations in the scope of the ICH M2 remit, i.e. the limitation of participants to pharmaceutical industry and regulators, the limitation to the three ICH regions and Canada, and the limitation to human therapeutics.

This had led to consideration of several options for a future process, ranging from changing nothing to abolishing the M2 EWG and transferring the work fully to Standard Development Organisations (SDOs). SDOs like the International Organization for Standardization (ISO), the Comité Européen de Normalisation (CEN), and Health Level Seven (HL7) have come about mainly due to FDA recommendations within ICH. In their last meeting in June 2006 in Yokohama, the ICH Steering Committee charged the M2 EWG with exploring the possibility of the formation of one or more consortia between ICH and SDOs to develop message standards. The first consortium to be formed will be between ICH and ISO, CEN and HL7. The basic idea behind a consortium is the linking into regional law. As an example, any standard for the EU must be "CEN-approved".

Electronic submissions

The major consequence of this shift to SDOs will be that message specifications will then be developed in an open environment. Anyone with an interest in the standard can participate: industry associations, individual companies, regulators, software vendors, etc. One of the major advantages of this approach will be that software necessary for support in the implementation will be almost ready when the standard is finalised. Today, actual software development to support the practical implementation of a message standard will only occur after the finalisation of the standard. Any draft specification poses too big a risk for software vendors in terms of major changes in the finalisation of the standard.

There are certainly risks as well. As an open arena will give ICH less control over the final standard, the actual process should be carefully constructed to maintain as many ICH controls as necessary and to limit commercial influence in the process.

It is anticipated that the next major release of the eCTD specification—version 4.0—will be developed in the ICH-SDO consortium.

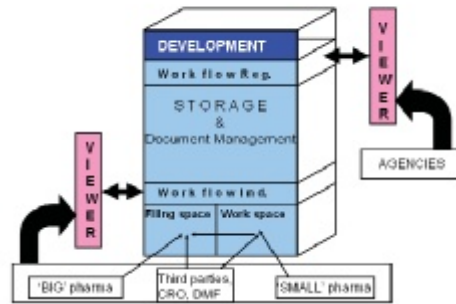
EU eCTD implementation

The current approach to implementation of the eCTD specification in the Member States and at the EMEA at different speeds is a logical choice. Nevertheless, it also contains a major risk that is already coming to the surface. National implementation actually means local portals for filing eCTDs using local application forms based on different technologies. In the end, this could mean that a pharmaceutical company in a European procedure has to go through many filing procedures, filing every time (slightly) different eCTDs in the different Member States. This is like the old situation with paper before the CTD. In the coming years, it will be crucial for Member States and the EMEA to bring their individual initiatives into line with each other or even to undertake joint activities in this area. In order to come to a solution, an idea from the beginning of the new millennium should be revived: an information broker, service provider, trusted third party or whatever one would like to call it should be part of the business process between regulators and industry. This trusted third party can have many roles and responsibilities:

- Provision of a secure ICT environment, available 24 hours a day, 7 days a week and access controlled
- Provision of work-flows
- Provision of document and dossier management, including records management and archiving
- Development, deployment and maintenance of databases: safety, product information, etc.
- Provision of filing and work space
- Development of standards, tools and systems

The possible activities of such an intermediate partner are illustrated in the following simple diagram.

Possible EU SP/OS-model:



However, the actual realisation of such a model is a huge task. There are legal, financial, technical and political issues to be resolved. However, although it might look impossible, the idea should seriously be further explored, investigated and elaborated because it might be the critical factor for a successful implementation of the eCTD in the EU.

Conclusion

Over the last ten years, much effort has been invested in developing electronic standards for the transfer of pharmaceutical regulatory information from industry to agencies. We have come to a point in time where all the prerequisites for successful implementation are now in place: business requirements, standards, software, implementation plans and clear business drivers. It is anticipated that the amount of actual electronic transfer of information in the pharmaceutical world will increase dramatically in the EU in the next few years. This does not imply that regulators and industry can sit back and relax. There is still much work to be done in streamlining business processes between the parties at the pan-European level. At the same time, technology will change, and those changes will have to be taken into consideration. The frequency of change in current standards and the development of new standards to be implemented will speed up through the new approach with SDOs. In other words, the next five years will be critical and exciting in this area of regulatory interaction.

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More Swift and more nets

The reasons why so few marriages are happy, is, because young ladies spend their time in making nets, not in making cages.

Jonathon Swift in Thoughts on Various Subjects (1711)