cunesoft
compliance delivered

API drug submission changes in 2016 and beyond

What FDA and EMA require for DMF/CEP/ASMF's

October 2016

API submission changes in 2016 and beyond - What FDA and EMA require for DMF/CEP/ASMF's

The eCTD (electronic Common Technical Document) guidance has been increasingly utilized by industry and health authorities for some time now. Almost nine years ago, the US FDA officially announced that the eCTD standard would be the preferred format for electronic submissions to FDA beginning January 1, 2008.

Health authorities in countries around the world have embraced the eCTD as well and have created an even stronger case for using the well-established format. The US FDA alone has received almost 100,000 eCTD submissions. When considering the adoption of this format by other health authorities as well, it can be said that the eCTD format has been a huge success both for industry and for regulators.

The benefit to the industry is apparent when one considers the impact of migrating paper based documentation and submissions to an electronic format. It offers regulatory benefits such as:

- Clear and implicit traceability of document creation
- Change control
- Working paperless
- Streamlining a very resource-intensive process

Companies utilizing the electronic creation, submission and archiving of regulatory documentation can decrease both internal review times and overall time to submission. In a very competitive market environment, these efficiencies can also lead to better collaboration between the industry and regulators and thus speed up overall time to market.

Many health authorities have announced plans to migrate the remaining paper based submissions to electronic models. In fact, as of May 5, 2017, NDA, ANDA, BLA and Master Files must be submitted in eCTD format to the FDA. For the EMA, eCTDs for centralized procedure types are mandatory already, for other submission types it is the recommended standard.

FDA – Update

In September 2016, the FDA published new deadlines on electronic submissions:

- **May 5, 2017: NDA, BLA, ANDA and DMFs must be in eCTD format**
- **May 5, 2018: Commercial INDs must be in eCTD format**

>>more information to the deadlines<<
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

After these key dates, companies will not be permitted to send paper and/or non-eCTD submissions. In some cases, an exemption may apply and further information regarding exemptions can be found here:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

The FDA update also described modifications for all electronic formats including the requirement for PDF forms will need to be fillable and electronic signatures must be used. Emphasis was placed on the correct use of lifecycle management to ensure that content such as study data is not submitted repeatedly.

Submission delivery is changing as well. After May 5th, CD-based submissions will not be accepted. Submissions less than 10GB will need to be transmitted using the online gateway. Larger submissions can be sent using a USB drive (physical electronic media) or the gateway.

The deadlines for standardized study data is the 17th of December 2016 (NDA, BLA and ANDA submissions) except for the IND submissions. Here the deadline is a year later – December 17, 2017. The Study Data Technical Conformance Guide can be viewed here:

http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

The technical rejection criteria for study data documentation is also available:

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

Finally, the CDER gateway third acknowledgement is now in place since the end of May 2016 and applies only to NDA, ANDA, BLA, IND or DMF submissions. The CDER acknowledgement is added to the ESG Message Delivery Notification acknowledgement (first acknowledgement) and the Official Center acknowledgement (second acknowledgement) and will be sent when a submission is ready for review and has successfully passed the validation and processing. The third message may be delayed if there are difficulties with the validation process and may also communicate the rejection of the submission.

Read more on the cune-Blog:

http://cunesoft.com/2016/10/14/fda-update-electronic-submissions-september-2016/

EMA – Update

The mandatory use deadline of the PSUR Repository has started on June 13th 2016. Only electronic submissions (eCTD or NeeS format) are accepted by the repository. It

is required to deliver an XML file as a zip file, which contains submission details such as procedure numbers, product names and information for routing purposes. The zip file for upload has to follow a specific file naming convention. Do you know, how to name your PSUR ZIP file correctly?

Please, have a look at our „PSUR Cheat-Sheet“:

http://cunesoft.com/wp-content/uploads/2016/07/Cheat-Sheet-5-minutes-Guide-PSUR-ZIP-File-Naming.pdf

Other Agencies

Health Canada	Since June 1st, 2016, they have stopped accepting paper copies of clinical trial regulatory activities and their related transactions. Moreover, they announced that January 1st, 2017 is the date for mandatory filing of all regulatory activities, as per the FAQ - CESG document, via the CESG for transactions under 10GB in size.
Swiss Medic	Currently accepts eCTD submissions
Japan PMDA	Currently accepts eCTD submissions
Saudi FDA (SFDA)	eCTD submission types are optional from 17th of July 2016 and will be mandatory from 01st of January 2017 onwards.
MCC South Africa	updated their eCTD QA in April 2016: http://www.mccza.com/documents/ddff69242.28_eCTD_QA_Feb16_v2-1.pdf
TGA Australia	Currently accepts eCTD submissions as of 2014. From the 1st of January 2016 all eCTD applications must be submitted to the TGA
ThaiFDA.	Currently accepts eCTD submission from May 2015 and announced to make e-CTD submissions mandatory from 2017

Migrating from Paper to eCTD – not as complicated as it sounds

Migrating existing paper based CTD submissions into a new electronic format sounds like intensive work and a daunting task at first. However, regulatory affairs professionals with experience using the CTD format can utilize the pre-defined structure immediately and can navigate the electronic structure with ease.

An eCTD software application is helpful in maintaining compliance with all specifications (specifically with the requirements of the targeted region where the submission is being made). A well-designed application is designed to validate the format and even part of the content for specific countries before the submission is

made to the authorities.

From a regulatory requirements point of view, the migration from paper to the eCTD is essentially a 2 step process as shown in the following example with FDA:

1. Submit your last paper based submission with a Form FDA 1571 as a general correspondence submission. Your cover letter should contain a note stating that you are intending to submit all further submissions in the eCTD format as well as the fact that you are starting with the eCTD Sequence Number 0000.
2. After filing your last paper based submission, you are sending your first eCTD submission, that contains only a Form FDA 1571 as well as a cover letter, stating that this eCTD submission is referring to the last paper based CTD submission and that all future submissions will be made in eCTD format.

After going through the steps outlined above you are in compliance from the regulatory standpoint – however, there are additional recommendations that are outlined here:

1. As you are moving from paper based submission to eCTD, there is high probability that your organization maintains direct and ongoing correspondence with the FDA and/or EMA. It follows that your organization keeps the agency's regulatory project manager apprised of your plans and works with him on the specific steps to take for your specific submissions.
2. Familiarize your organization with the eCTD guidances and eCTD management systems before moving to the new specifications.

Conclusion

Authorities around the world are quickly moving towards requiring full electronic submissions. The eCTD is already the mandatory way of collaborating and submitting documents to many of them and has been designated as the preferred method (even if it is not explicitly required) for others. For many regulatory submissions to FDA and EMA, the eCTD is already required. There are clear timelines from both agencies to make the eCTD the mandatory submission method for most applications.

As a "Head of Regulatory", we advise you to put an electronic submission plan in place at least 6-12 months prior to making your first eCTD submission.

Contact Us for more information and Product Demo:

Cunesoft GmbH
Luise-Ullrich-Strasse 20
80636 Munich
Germany
Phone: +49 (0)89-235 14741
Website: www.cunesoft.com
Email: info@cunesoft.com

