

BfArM rule changes

for the submission of applications in electronic format

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Keywords

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Abstract

From 31st March 2010, the Federal Institute for Drugs and Medical Devices (BfArM) has accepted virtually paperless electronic-only submissions for new applications for the authorisation or registration of medicinal products, as well as for post-authorisation procedures (eg, variations, renewals, periodic safety update reports) for those medicinal products already submitted under the new rules after 31st March.

BfArM is currently aligning its internal processes to be able to accept electronic-only submissions for post-authorisation procedures for all medicinal products in the near future. This preparatory work can be supported by applicants switching their submission formats to either the Electronic Common Technical Document (eCTD) or the Non-eCTD Electronic Submission (NeeS) format, validating their submissions in advance, and submitting the validation report voluntarily. BfArM will inform applicants well in advance about widening the scope. This article explains the rule changes and BfArM's expectations and requirements related to these changes.

In general, BfArM now prefers electronic submissions of new applications in eCTD format (two copies of electronic media) according to the published specifications of EU Module 1 and ICH Modules 2 to 5. Detailed information about the structuring and formatting of eCTD submissions is available on the European Medicines Agency (EMA) website.

BfArM will also accept Non-eCTD Electronic Submission (NeeS) (2 copies of electronic media) according to the requirements set out in the NeeS Guideline, resulting in missing the XML backbone of the eCTD format. Detailed information about structuring and formatting of NeeS are available on the EMA's website (for references follow the links at the end of this article).

The use of other electronic formats for electronic submissions is not acceptable and such submissions will still require a complete paper dossier. In cases where the electronic submission is not structured according eCTD specifications or NeeS requirements, or if a company prefers to submit a paper dossier or is not using the PharmNet-Bund-Portal for electronic variations, the company will still need to follow the AMG-Submission Ordinance (AMG-EV). However, it needs to be stated explicitly that the submission of dossiers in paper format is still an option. Despite the clear preference for receiving submissions in electronic format, this is not currently mandatory.

Even in cases where dossiers are submitted in electronic format according to the aforementioned rules, some 'wet signed documents' need to be submitted on paper, ie, the Cover Letter (Module 1.0 CTD including a printout of the 'History of Sequences'), the Application Form (Module 1.2 CTD including Annexed Documents) and the Declaration of the Experts (Module 1.4 CTD). In addition, applicants must request the so-called Eingangsnummer¹ (ENR, a procedure number) in advance. Moreover, applicants

must provide a printout of the report of their own technical validation² (see below for further information).

Some practical details

Before sending CDs/DVDs, a company must be sure that its data can be read correctly. (CRC errors, which may occur during copying the data, must be resolved before submission.)

The root directory must be named by the procedure number (eg, the national ENR or the main part of the DCP number and the national ENR) or the name of the medicinal product following the rules for naming leaf titles within the eCTD (see Figure 1a). The product structure should be mirrored accordingly.

Underneath the root directory the sequence folder and a folder for working documents should be created (see Figure 1b). Working documents are understood as those which are required to be submitted by the submission ordinance AMG-EV, namely Module 1.3.1 and Module 2, and should generally be provided in 'rtf' format. The folder is named "<sequence>-workingdocuments" and replaces an additional separate submission according the AMG-EV ordinance.

If a submission concerns multiple applications or authorised products (eg, several ENRs) the respective folders have to be created named by <procedure number.> or <ENR> (eg, de-h-09999-001, de-h-09999-002 etc.).

Typically, an eCTD/NeeS application will cover all dosage forms and strengths of a product with any one invented name. In MRP/DCP, a single eCTD/NeeS application should preferably be used for each procedure (eg, DE/H/1005/001-002/DC). However, if the applicant decides to have one NeeS per strength or dosage form, this would also be acceptable but should be carefully considered in relation to transformation into eCTD at a later stage.

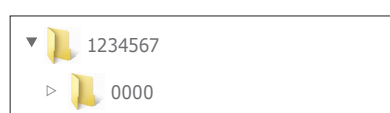
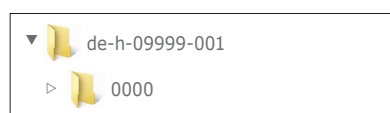
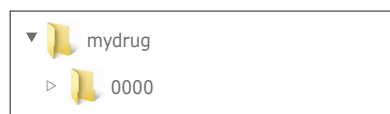
Figure 1: Elements of a standard eCTD folder structure/NeeS submission

(A) Root directory requirements

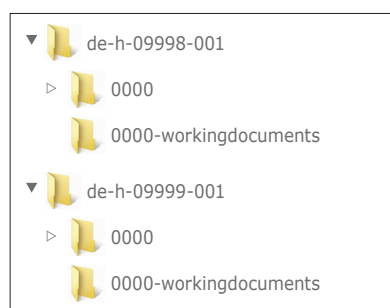
Preferred naming of the root directory



Alternative options naming the root directory



(B) Sequence folder and working documents folder



(C) NeeS format including hyperlinked table of contents

Folder	Name
de-h-09998-001	m1
0000	m2
m1	m3
m2	m4
m3	m5
m4	ctd-toc.pdf
m5	
0000-workingdocuments	

Applicants should carefully consider what an eCTD application should cover before submitting the first sequence, as the choice could have implications for workload for the lifespan of the product. For example, if the applicant decides to have one eCTD per strength or dosage form, it is expected that each of these eCTD applications will be maintained individually, such that submission of a single sequence that covers more than one strength or dosage form will no longer be possible if very good reasons are not presented for a change. In these rare cases, applicants should contact BfArM when the agency is the RMS at an early planning stage. In such cases, only the main part of the procedure number to name the root directory can be used. However, the documents required on paper need to be submitted per application until further notice.

In cases where several sequences should be submitted per one CD/DVD, the respective sequence folder must be created.

With the NeeS format, access to all single documents needs to be guaranteed by a hyperlinked table of contents, 'ctd-toc.pdf' (see Figure 1c). This may refer to more detailed tables of contents of each module in the case of very large submissions, or to each single document of the entire dossier in the case of smaller dossiers.

In the cover letter, all medicinal products applied for and for which the eCTD/NeeS submission is valid need to be stated, including the procedure number/ENR. The electronic format needs to be specified as well as the number of discs/hard media. A contact email address is essential so that the agency can send confirmation of receipt or the report of technical validation.

At any time an electronic submission in eCTD or NeeS format is submitted, an updated 'History of Sequences' named as 'tracking.pdf' needs to be present in the same folder as the cover letter, as well as a printout. This will support transparency and ease tracking of sequences regardless of the format.

Technical validation

Before submitting a dossier applicants must perform a validation to check that their dossier really complies with the requirements mentioned above (ICH M2 eCTD v.3.2.2, EU M1

v.1.4; NeeS file and folder naming convention, PDF configurations) and that any errors have been eliminated.

BfArM offers, free of charge, the download and use of a tool which proves an applicant's dossier against validation criteria for eCTD format as well as for NeeS compilations and PDF files (file size, PDF version, configuration, hyperlinks, bookmarks, naming conventions). The tool offers basic functionalities according to the current specifications of eCTD EU M1 v1.4 and ICH M2–M5 v.3.2.2 (Validation criteria v2.1) as well as of NeeS (Validation criteria v1.0); the default settings are in accordance with BfArM requirements. Further technical support for using the BfArM-eValidator is not available.

Use of the BfArM-eValidator is based on a general licence with no charge or registration needed from the user. The end-user licence agreement can be downloaded and reviewed in advance, separately, before installing the software.

In any case BfArM will itself perform a technical validation. Applicants will be informed if errors or warnings are highlighted. Therefore, the email contact information is essential to allow the agency to send back the validation report. Any term will start immediately following a successful technical validation.

Errors indicate an unsuccessful technical validation. The check-in procedure will be set on hold until the applicant's submission is corrected (a new version of that same sequence).

Warnings will be ignored for check-in, but the applicant will be informed to support future improvement. Although BfArM recommends use of the BfArM eValidator, the use of other validation tools available on the market will be meaningful as long as they comply with the published validation criteria. However, due to experienced differences by interpreting some of the criteria differently the selection of the most appropriate tool should be taken carefully.

Making use of the option to submit applications in electronic-only form, an applicant will need to declare acceptance of the following rule:

CDs or DVDs submitted will be checked for their compliance with technical specifications

(of the eCTD or NeeS) prior to the start of the content-related validation. Only in the event of a positive outcome of the technical validation – at least after the applicant has resolved technical deficiencies – can the receipt of the application be confirmed. At that point the content-related validation will start. The applicant will receive a confirmation of the start of the validation period.

Future expectations

Despite long-term experience with electronic formats and intensive discussions about the necessary features for reviewing tools in Germany as well as on a European level, moves to convert paper-based submissions into a structured electronic format according to agreed international standards have been relatively slow in the past decade. To some extent the commitment of the Heads of Medicines Agencies to accept e-only submissions by the end of 2009 has introduced some drive. But the decision to request e-only submissions in eCTD format by the EMA for centralised procedures has caused some pressure within the European Network of Agencies, while the willingness of industry to change its processes has grown. The number of eCTD and NeeS submissions has increased considerably, in addition to the centralised procedure, and namely for the newly introduced decentralised procedure. Agencies are all on the upwards slope of a learning curve. There will be no real alternative to this new way of working and several advantages will be achieved, including the reduction of (internal) paper-flow (the logistics and administrative burden); the reduction of physical archiving space and the facilitation of the review process. In addition, other aspects from both the regulator's and industry's perspective will see similar improvements, eg, the quality of the dossier; flexibility to support different regional specifications and other formats; ease of logistics and ease of archiving. Despite the current complexity, several proposals for simplifying lifecycle management and supporting two-way communication are under discussion and serve as the main driver of a next major version of the eCTD spec, presumably in cooperation with HL7 and aiming to

become an ISO standard. However, the electronic way of exchanging information and assessing data supported by electronic review systems will be maintained and surely improved over time. Other systems, for example the European Product Information Management (PIM) system, will be added or integrated. Internal systems of the agencies and the use of portals or gateways will need to inter-operate with common review tools or centralised repositories. A single point to upload data will be another feature requested by industry. Clearly, close collaboration between all interested parties is essential and can hopefully be achieved to the advantage of all stakeholders.

Notes

- 1 Prior to filing an application, send an informal letter, preferably by fax to BfArM, Fachregistratur Z14.1, (Fax +49 228 207 3681) giving complete contact details of the applicant, name + pharmaceutical form + strengths of the product, and request an ENR (Eingangsnummer) – a procedure number that must be referred to in all further communication with the agency.
- 2 The term 'technical validation' has been used in this article and in all documentation related to electronic submissions on BfArM's website. The meaning of this term in all instances is 'to check the published technical specifications of the submitted electronic media (the German legal term is 'Spezifikations-Überprüfung)'. This technical validation needs to be clearly differentiated from the content-related validation according to §25a AMG (German Medicines Act).

Bibliography

A number of relevant documents can be found under the 'Documentation' tab on the EMA's e-submission webpage. It is recommended that, because the information is continually changing, the following websites should be consulted regularly:

- <http://estri.ich.org/eCTD/index.htm>
- http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index_en.htm
- <http://esubmission.ema.europa.eu/index.html>

- <http://www.hma.eu/277.html>
- http://www.bfarm.de/cln_012/nn_1198796/DE/Arzneimittel/2___zulassung/zulVerfahren/eSubmission/eSubmission.html

Important documents to be considered are the following (as of 1 May 2010):

- http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf
- http://estri.ich.org/eCTD/eCTDQAV1_18.xls
- http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-2/index_en.htm
- EMA Q&As. <http://www.ema.europa.eu/htmls/human/genguidance/genreg.htm>
- BfArM eSubmission Q&As. http://www.bfarm.de/cln_012/nn_1198796/SharedDocs/FAQ/DE/Functions/am/eSubmission/faq-eSubmission-table-gesamtansicht.html
- ICH M4. <http://www.ich.org/LOB/media/MEDIA554.pdf>
- CH M4 Q&As. <http://www.ich.org/LOB/media/MEDIA1189.pdf>
- EU CTD Q&As. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_qa_05_2006.pdf

About the author

Dr Klaus Menges is currently responsible for 'Process organisation and scientific quality assurance' at BfArM. This role focuses on the content aspects of assessments but also covers all authorisation processes, especially the electronic submission and the electronically supported product information management (PIM).

Previously, he has been the Head of Unit, Neurology and Psychiatry (1988-1996), and Head of Unit, Algesiology, Anaesthesiology (1996-2005), of the 'Clinical Pharmacology II' Section at BfArM.

He has long-term expertise on drafting and assessment of package leaflets. In his current position he has become familiar with readability testing, especially with its principle assessment aspects.

Dr Menges represented BfArM in the Assessment Training Workshop on Readability Testing Reports at the European Medicines Agency, and he is a member of both the TIGes and the PIM steering committees.