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**INSTRUCTIONS OF THE
SLOVENIAN AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL
DEVICES**

**INSTRUCTIONS FOR eCTD and NeeS SUBMISSION
AND VALIDATION CRITERIA**

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TERMS AND DEFINITIONS

Antivirus program: Program detecting and eliminating computer viruses and preventive security measures against them.

Baseline submission: eCTD sequence, which contains an electronic baseline submission, which is the same as the paper documentation on the basis of which a pharmaceutical has already acquired market authorisation or a variation made. A baseline submission must be identical to the paper form and serves to provide easier monitoring and review of subsequent submissions in eCTD format, such as market authorisation variations and renewals and other submissions.

Bookmark: Link highlighted within a document.

eCTD (Electronic Common Technical Document): International standard describing rules for producing and sending electronic submissions for pharmaceuticals for human use.

Electronic submission: Each individual document submission in eCTD or NeeS format.

Envelope: XML computer record, which is part of the eCTD standard and contains administration data on an individual electronic sequence.

eValidator: Program tool from the Lorenz company, which is used to verify the compliance of electronic submissions with the validation criteria.

Fast Web View: Property of documents in PDF format that enables the transmission and display individual documents section (pages) only, instead of the entire document.

Folder: In a computer record, a folder includes documents and other folders.

Hyperlink: Connection supporting a jump to a different part of a text or web address.

Initial sequence: First electronic submission in eCTD for a specific pharmaceutical, generally labelled as 0000.

NeeS (Non-eCTD Electronic Submissions): Recommendations for preparation and submission in electronic formats similar to the eCTD. Unlike eCTD, NeeS does not include an envelope or XML backbone. Instead it uses a PDF format index that includes links to individual documents that are constituent parts of a submission. NeeS recommendations are regional and only applicable in the EU.

OCR (Optical Character Recognition): Conversion (scanning) of text image to text that can be searched and formatted.

PDF (Portable Document Format): Document format that supports exchange of texts in unchanged form. Software from Adobe is generally used for production and reading of these texts.

RTF (Rich Text Format): Document format with basic formatting elements, enabling simple exchange of formatted text between different text processors.

Sequence: Each individual submission in eCTD format. A sequence is located in a folder named with a 4-figure code. The sequence for a specific pharmaceutical must be located in the same folder as the pharmaceutical.

Subfolder: Folder included within another folder.

Text searchable documents: Documents supporting content search, highlighting and copying of sections of text.

Top folder, Root folder: Folder containing all sequences for a specific pharmaceutical.

Tracking table: A table providing a list and method of use for sequences linked to a specific MRP/DCP procedure.

Validation: Procedure using specialised software to test submission compliance with validation criteria. The result of validation is a report describing any non-compliance and their significance in terms of the validation criteria.

Validation criteria: List of rules defining submission compliance with recommendations and standards that apply to submissions in eCTD and Nees formats.

XML (eXtensible Markup Language): Computer language for description of data and structured documents.

1. Introduction

The purpose of this document is to describe the technical requirements and rules enabling applicants to prepare and send electronic submissions.

The instructions in this document apply to submissions for pharmaceuticals for human use.

The instructions do not apply to submissions for pharmaceuticals for veterinary use, traditional herbal medicines, homeopathic medicines and medical devices.

The Slovenian Agency for Medicinal Products and Medical Devices (the Agency) has introduced an information system supporting the adoption, review and archiving of electronic submissions. The system is based on Lorenz docuBridge technology and is in compliance with EU standards and practice.

Electronic submissions must comply with EU standards and recommendations. The Agency reviews every submission on receipt using a validation tool and (Lorenz eValidator) and antivirus program.

The Agency advises all applicants to validate their submission with the same software before sending to avoid subsequent complications.

The Lorenz eValidator software (basic version) is available free-of-charge from the website of the Lorenz company: www.lorenz.cc

If validation fails, the Agency acts in accordance with Article 67 of the General Administrative Procedure Act (Official Gazette of the Republic of Slovenia, no 24/06 – consolidated version, 105/06-ZUS-1, 126/07 and 65/08).

The Agency will treat submissions infected with a computer virus in the same manner as submissions that fail validation.

The document has been produced in accordance with the current state of procedures to acquire and renew market authorisation for pharmaceuticals for which documentation is submitted electronically. The Agency reserves the right to amend the document in accordance with changes in the area, as required.

1.1 Schedule

The Agency will handle eCTD and Nees formatted submissions in line with these instructions from 1 January 2010 onward.

A transitional period will be in force at the Agency from 1 January 2010 to 31 December 2010.

Table 1 indicates the requirements by individual submission format:

Submission format	Documentation that must be submitted in specific submission format from 1 Jan 2010 to 31 Dec 2010	Documentation provisionally to be submitted in specific submission format from 1 Jan 2011 onward
Submissions on paper	1 x Full documentation (modules 1-5) on paper	1 x Full documentation (modules 1-5) in eCTD or NeeS format
eCTD	1 x Full documentation on CD/DVD, module 1 on paper	1 x Full documentation on CD/DVD
NeeS	1 x Full documentation on CD/DVD, module 1 in paper format	1 x Full documentation on CD/DVD
Other formats with documentation in electronic form	1 x Full documentation on CD/DVD, module 1 in paper format	After 1 Jan 2011 the Agency will provisionally no longer accept documentation in electronic formats other than eCTD or NeeS

Documents in paper format must be in the same order as the electronic documents.

In case of changes, the Agency will publish new instructions on electronic submission before the end of the transitional period.

1.2 Types of Procedure and Submission

The Agency accepts the following types of submission in electronic format (for MRP, DCP and NP procedures):

- Acquisition of pharmaceutical market authorisation
- Extension of existing pharmaceutical market authorisation
- Renewal of pharmaceutical market authorisation
- Variation of pharmaceutical market authorisation market authorisation
- Periodic Safety Update Report (PSUR).

In future the Agency will still accept submissions in paper form.

1.3 Transition to Electronic Format

Applicants deciding to send submissions electronically must also send all subsequent submissions relating to the same pharmaceutical in electronic format. This means

submitting subsequent submission in paper format for the same pharmaceutical is no longer possible.

A transition from the NeeS format to the eCTD format is possible, but the opposite is not. A transition from paper is possible to either NeeS or eCTD. A transition from electronic format to paper is not possible.

2. Technical Specifications

2.1 General Instructions

The electronic data-carrier for electronic submission must be a CD or DVD that meets ISO 9660 or ISO 13346 specifications.

The data-carrier must not be damaged or soiled.

The data-carrier must be protected with a protective cover without a label. Each data-carrier must be labelled with the following data (printed on a sticker on the surface of the data-carrier):

- Applicant's name
- Proprietary (invented) and non-proprietary name of pharmaceutical
- Type of procedure and submission
- Format and version of electronic submission format (eCTD version..., NeeS)
- Procedure number for specific pharmaceutical (if available)
- Number of sequences on data-carrier and brief description of individual sequence (applies only to eCTD submissions)
- Date of sequence input (DD-MM-YYYY)
- Number of data-carriers in package and carrier serial number within package.

The contents of the electronic data-carrier must be checked with antivirus program.

The content of an electronic submission must match the content of the same submission in paper format (Module 1), and the documents must be submitted in the same order in both formats. The data-carrier must include a copy of all documents in the documentation in paper format, and vice versa.

The data-carrier must not have any content that is not a constituent part of the submission.

Applicants that send electronic submissions must take into account the applicable specifications and instructions (links to these documents are found on the Agency website):

- Instructions mentioned up in this document
- EU Module 1 Specification, version 1.4, August 2009
- Electronic Common Technical Document Specification
- CMD(h) Best Practice Guide on the use of eCTD in the MRP/DCP
- Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD Electronic Submissions
- Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (Nees).

The Agency does not accept submissions saved on hardware (portable computers, ZIP carriers, etc.). In the case of large submissions we recommend the use of one or more DVDs, instead of a CD. If it is not possible to use a single data-carrier, we recommend that the content of an individual module must all be on the same data-carrier. If the content of one module cannot be saved on one data-carrier, the content must be divided between data-carriers in a manner that ensures that the content of individual folders within a sequence is not divided between two data-carriers.

In addition to the requirements stated in the Rules on Market Authorisation for Pharmaceuticals for Human use (Official Gazette of the Republic of Slovenia, no 59/06), the cover letter must state the following data:

- content of data-carrier (specifying pharmaceutical, type of submission, type of procedure)
- data-carrier format (CD, DVD)
- number and content of individual data-carrier
- statement that data-carrier content (CD/DVD) has been verified with an antivirus program (name of antivirus program and version)
- type of validation tool used to test the electronic submission before being sent to the Agency (name of validation tool, version)
- contact person to manage submission validation problems
- statement that the documentation submitted in paper form is identical to the documentation submitted electronically
- statement that documents in electronic format only different from those on paper in the fact that they have not been signed.

For MRP/DCP procedures we recommend the use of the cover letter template published on the CMD(h) website. Originally signed cover letter and the application form must be in Slovenian language.

2.2 Content of CD/DVD Data-Carrier

The applicant is initially free to select any name for the root folder (top folder), but subsequently the root folder name cannot be changed.

Each subsequent submission or supplement to a submission for a specific product (in the form of a new sequence) must use the same root folder name.

The content of an individual electronic submission in eCTD format must be saved in a subfolder (within the root folder) with a serial number in the form of a four-digit code (sequence folder).

The subfolder in the first electronic form (initial sequence) generally starts with the code 0000 (initial sequence: 0000). Each subsequent submission is contained within a subfolder (sequence) with a higher serial number.

2.3 eCTD Envelope

The data in an eCTD envelope is extremely important for handling electronic submission, since it links individual eCTD sequences. Data must be entered to the envelope in line with the applicable specifications for Module 1.

Envelope data must be accurate and relevant throughout the pharmaceutical life cycle.

2.4 PDF Documents

PDF (Portable Document Format) documents should be prepared as text searchable documents.

When possible, documents should be prepared from the original electronic form, usually MS Word. In this manner documents preserve all their features and their size is as small as possible.

Another possibility is preparing PDF documents on the basis of optical scanning of original paper documents. In that case, optical character recognition of the text must be carried out. Due to the relative complication of OCR, not all original paper documents have to be OCR-processed.

The list of key documents that must be text searchable:

- cover letter, form, information on pharmaceutical
- entire quality summary, summary and review of non-clinical documentation, summary and review of clinical documentation
- main sections of texts and tables in non-clinical and clinical reports enclosed with support documentation
- main sections of Module 3 data
- main sections of data from Periodic Safety Update Report (PSUR)

- main section of data from Risk Management Plans (RMP)
- main section of data from Environmental Risk Assessment (ERA).

The list of documents for which searchable text content is desirable, but not required:

- GMP certificates
- analysis certificates
- manufacturing licence
- European pharmacopeia Certificate of Suitability (CEP)
- translations of documents listed above, if in a foreign language.

PDF documents must meet the following requirements:

- documents (files) must be saved in PDF format version 1.4 (Adobe Acrobat 5.0)
- documents must not be password-protected and must enable “Fast Web View”.

In specific cases, PDF documents may be saved in another version of PDF. The use of another format must be justified in the cover letter.

In cases in which optical scanning of a document cannot be avoided, a resolution of 300 dpi (up to 600 dpi for photographs) and black/white scanning. We do not recommend colour or grey-scale scanning, in order to reduce the size of individual optical scanned documents.

The size of an individual document (file) should not exceed a maximum of 100 MB.

More detailed additional instructions relating to PDF documents are given in the ICH eCTD Specification Document, Appendix 7.

2.5 Hyperlinks and Bookmarks

The logical use of hyperlinks and bookmarks is recommended in the production of electronic submissions. The hyperlinks and bookmarks should enable a quicker overview and easier orientation within the submission. For more detailed instructions on the use of hyperlinks and bookmarks, see “Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD Electronic Submissions” and “ICH eCTD Specification version 3.2.2”.

2.6 RTF Documents

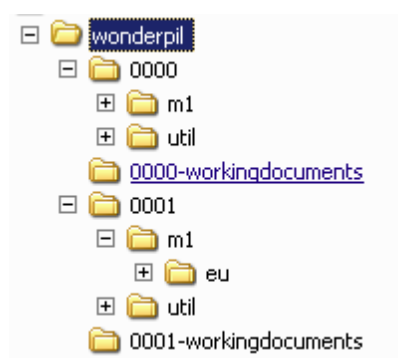
In addition to documents in PDF format, the Agency also requires documents in the RTF format to facilitate assessment:

- Module 1.3: Product information.

RTF documents should not be included in the NeeS or eCTD XML backbone and eCTD folder structure, since they are exclusively intended to support the work of the Agency's specialist staff.

RTF documents should be saved in a separate folder "<sequence no>-workingdocuments" – on a CD/DVD with eCTD:

Example:



RTF documents must have the same name as the PDF documents, only being differentiated by the extension (.rtf instead of .pdf).

The documents must be on the same data-carrier as the eCTD sequence.

3. Validation

3.1 Validation of eCTD Submissions

Electronic submission content (sequences) must be located in the root folder (top folder).

If a submission is technically invalid (errors detected during validation), a new, technically valid submission with identical content must be included in the subfolder (sequence) with the same serial number, replacing the original, invalid sequence.

If a submission is technically valid, but the content is not valid, a supplemented submission must be submitted in line with the requirements of the Agency's

specialist staff or RMS (reference member state) staff in the case of MRP/DCP procedures, with a new (higher) serial number and appropriate cover documents. A submission supplement therefore supplements the prior documentation. The supplement envelope must state which sequence it supplements – labelled as “related sequence.”

For sequences with a sequence number higher than 0000 and with metadata containing information on a related sequence, prior submissions (sequences) must already exist, and the applicant must submit them to the Agency if the mentioned sequences have not already been sent in a submission. In that case the Agency must be notified on when and in which submission the prior sequences were submitted. The new submission envelope must state which sequence it supplements – labelled as “related sequence.”

The names of documents in the eCTD structure for Module 1 should be descriptive, so that Agency specialist staff can already see the document type from the document name. Document names in the remaining modules must be in line with the applicable ICH standard.

The Tracking Table must contain relevant and correct information.

3.2 Validation of NeeS submissions

NeeS format submissions will be checked with an antivirus program and subject to validation.

3.3 Validation Criteria

The validation criteria for eCTD are described in the document EU eCTD Validation Criteria v2.1 April 2009.

The validation criteria for NeeS are described in the document EU NeeS Validation Criteria v1.0 August 2009.

The Agency carries out validation using the Lorenz software tool Lorenz eValidator.

An interpretation of the validation criteria is provided as part of the tool documentation and described in the documentation:

- LORENZ eValidator – EU eCTD Validation Criteria.pdf
- LORENZ eValidator – EU NeeS Validation Criteria.pdf.

4. Baseline Submission

The baseline submission contains the full documentation (Modules 1-5) for a specific pharmaceutical in electronic format (eCTD), together with the cover letter. The baseline submission for a specific pharmaceutical is submitted just once, and provides an overview of the full documentation for a specific pharmaceutical in electronic format.

A baseline submission is not required for pharmaceuticals for which the applicant has already acquired market authorisation.

The Agency does not treat a baseline submission as a procedure, therefore payment of administrative fees and charges is not required.

Despite this, the Agency recommends that base submission be made in eCTD electronic format for Module 3 (the baseline submission in that case constitutes the cover letter and full documentation for Module 3, applicable at time of submission), mainly for easier and faster subsequent amendment. In that case, the applicant must submit a statement to the effect that the documentation in electronic format is identical to the documentation previously submitted in paper format or in another electronic format and approved by the Agency.

We recommend that the baseline submission is the first sequence (0000), submitted in eCTD format, to be followed by new submissions for pharmaceuticals.

5. Frequent Errors

The Agency will publish errors that frequently occur during submission validation on its website. Applicants should take these into account.