

**Guideline on the specifications for provision of an electronic submission (e-submission)
for a veterinary medicinal product**

1. Introduction

This Guidance Document is intended to assist applicants and regulators with submissions of dossiers in electronic format. It specifies the basic parameters required for an acceptable electronic submission. The document has been created by the TIGes-Vet Sub Group which is made up of representatives from National Competent Authorities, the EMEA and industry. All National Competent Authorities should adopt this guidance as the basis for their acceptance of electronic submissions for marketing authorisations from applicants.

Answers to questions, variations, line extension, and renewal applications can be submitted in electronic format, i.e. as PDF files with no additional paper copies. The same basic principles apply except dossier structure, which may not be relevant for all these procedures.

The guideline builds on the specifications agreed in the TIGes-Vet Sub Group guideline of September 2007 by the addition of a specification for the folder structure (the granularity) to be used in a basic electronic submission to be known as VNeS. The guideline also introduces the option to prepare an electronic submission using a bespoke software package of which there are a number on the market. This type of submission is identified as an eNTA submission and is based on an XML backbone. An agreed technical specification for the eNTA will be developed at a later date.

2. Background

In 2005 the Heads of Medicines Agencies (HMA) agreed that all Member States would be able to accept electronic-only submissions by the end of 2009. The benefits of moving to e-working were seen as:

- reduction of (internal) paper-flow (logistics and administrative burden)
- reduction of physical archiving space
- product lifecycle management
- facilitation of the assessment and review process

At a meeting in July 2007 the HMA recorded the following decision, “In response to a direct request from industry, HMA confirmed that the requirement for agencies to be in a position to accept electronic only submissions by 2009 applied to veterinary as well as to human applications. It should be understood that the investment of resources by the Industry will also depend on progress made by the agencies.” This decision meant that agencies had to be able to accept electronic submissions from 1 January 2010 as well as continuing to deal with submissions based on paper.

3. Media used for submission and its identification

Appropriate labels/identification should be attached to the hard medium on which the e-submission is presented. This should include at a minimum: Name of the product, type of application, any procedure number, company, target species (if applicable), version (including date) and indication as to whether multiple media components are used (and if so, these should be numbered).

As a general rule, exchange of electronic files can be made on finalised optical media such as CD or DVD. Eudralink has a 40 MB limit and as a result it is unlikely that an e-submission of a complete dossier can be made by this means. Eudralink can be used for email communication with the authorities.

For authorities requiring an official signature for legal reasons, an originally signed cover letter or application form may accompany or follow the electronic submission.

If more than one CD or DVD is needed, the dossier should be split at a logical point within the granularity such that the integrity of the granularity is maintained.

Submission of product information (SPC, label, leaflet) in an editable format as an addition to a read-only file within the e-submission is encouraged. The location of these documents within the e-submission is set out in section 6.(c). It is also acceptable to submit these documents via e-mail.

4. Language

In order to facilitate the processing of the application and make the assessment more efficient, the scientific and technical documentation should be submitted in English. Both applicants and authorities should refrain from translations to languages other than English as this makes quality control and validation difficult and less reliable.

5. File Format & Source

All documentation should be submitted using file formats that facilitate both reviews on screen and paper while retaining a similar format.

The portable document format (PDF) is a format which supports the described features. PDF has been accepted as a standard for providing documents in electronic format by the International Conference on Harmonisation (ICH) and will be considered by the veterinary equivalent (VICH).

The PDF format used for a submission should be compatible with the baseline format PDF 1.4. The applicant should however check in cases where later versions are used that files do not use features specific to later PDF versions than 1.4 that may be lost or not viewable based on PDF 1.4 and thus potentially could change the visual appearance of the document. Applicants may offer, and agencies may request newer file formats but neither should be constrained to supply or accept anything other than files compatible with PDF 1.4 (or as updated by the ISO norm).

All PDF files should be created using software that allows reading and printing using a version that is available to companies and authorities. To ensure that PDF files can be accessed efficiently, PDF files should be no larger than 100 MB. PDF files should be optimized for fast web view (to enable reading the beginning of a file while the rest of the file is still being accessed).

6. (a) Paper source documents

PDF documents submitted as scans should be scanned at resolutions that will ensure the pages are legible both on the computer screen and when printed. Normally 300 dpi gives good results without compromising file size for text; higher resolution may be required for graphics. Applicants should ensure that the quality of the renditions is adequate for regulatory review.

6. (b) Electronic source documents

Where practicable, PDF documents should be created (rendered) directly from their electronic source documents. This allows functionality such as text searching, copying and pasting into editable formats.

- **Fonts for electronic source documents**

All fonts used in the document should be embedded in the (PDF) files to ensure that those fonts will always be available to the reviewer. All classical fonts are acceptable as well as True Type or Adobe Type 1 fonts in the case of PDF. It is recommended not to use proprietary fonts and to avoid customized fonts.

When embedding fonts, all characters for the font should be embedded, not just a subset of the fonts being used in the document. Embedding fonts requires additional computer storage space. To help limit the storage space taken by embedding fonts, applicants are encouraged to limit the number of fonts used in each document.

Font point sizes should ensure on-screen readability, for example 11-12 for normal text, 9-10 for tables and 8-10 for footnotes. The recommended font colour is black. The recommended fonts are Arial (11) and Times New Roman (12). Blue font can be used for hypertext links.

- **Page Format and Numbering for electronic source documents**

The print area for pages should fit on ISO 216:2007 A4 sheet of paper with sufficient margins with the exception of the mock-ups for packaging components which may require other formats. Pages should be properly oriented to reduce the effort of rotating pages. Pages within a file should be numbered.

6. (c) Documents to be edited

In the case that product information (such as SPC, labels and leaflet) are intended for frequent exchange, editable formats like Microsoft WORD might be supplied to facilitate transfer of documents with the ability to track changes. It is preferable for these documents to be included in a separate folder at the level of the root folder (see section 8. (a)). However, it is

also acceptable to include these in the folder for Part IB of the dossier. In the case of submissions of the same document in multiple formats (e.g. PDF and WORD at the same time), it should be clear which format is intended for which purpose. This clarification could be achieved by including a descriptor of the file types in the Table of Contents (TOC) for that part of the dossier.

7. Signatures

The applicant has the obligation to ensure a proper certification of the submitted documents. Valid signatures should be available from the applicant and be presented at the request of the authorities. National Competent Authorities should, wherever necessary, accept a signed paper cover letter confirming the correctness of the submitted file(s).

8. Structure of the electronic submission

8. (a) Folder structure

The folder structure (granularity) for an electronic submission is shown in Table 1 for pharmaceutical products and Table 2 for immunological products. The structure is based on the Notice to Applicants Volume 6B as amended by Directive 2009/9/EC¹ (Annex I to Directive 2001/82/EC as amended). The hierarchical structure of folders gives three levels of granularity and should be used to prepare the electronic submission. The folder structure includes a folder in the root folder for documents such as editable versions of the SPC and literature and documents which need to be provided at a local level (e.g. by a local affiliate of a centrally organised regulatory affairs department).

Including additional folders within the structure of the e-submission is not permitted. However, if there are empty folders in the submission these may be deleted as the folder structure should reflect only what actually is submitted. The relevant TOC should indicate in such cases that no data are being submitted for these sections of the dossier and that the respective folders have been deleted. When little or no information is presented for a number of folders at the same level of granularity it is acceptable to include all the information in a single PDF at the higher level of the granularity. Again this should be indicated in the TOC.

As discussed in the Introduction to this guideline this folder structure should be used to prepare a dossier in a basic electronic format (a VNeS). The folder structure also forms the basis for preparation of an electronic submission using a bespoke software package (eNTA). An agreed technical specification for the eNTA will be developed at a later date.

Folder names should be in English and follow the conventions given in Table 1 for pharmaceutical products and Table 2 for immunological products. Folder names created by the applicant may be abbreviated (e.g. in order to meet the maximum character limit for path length) as long as names are self explanatory and allow unambiguous identification according to the NTA structure given in Table 1 and 2 below.

¹ The folder structure and naming convention has of necessity been prepared before the publication of the final revised Volume 6B on Presentation and Content of the Dossier based on the new Annex to Directive 2001/82/EC. The folder structure and naming of folders may need revision after publication of Volume 6B.

8. (b) Indexing

The electronic submission must include a well-structured (preferably PDF format and hyperlinked) general table of contents (GTOC) in the root directory as well as a TOC in each folder for each part of the dossier. The GTOC should be a complete index to the whole dossier while the TOC for each part of the dossier should be a complete index for that part of the dossier.

8. (c) Files

Size and number

The number of files should reflect the size of the dossier. Individual files should not be bigger than 100 MB. The lowest level of granularity of the dossier structure shown in Tables 1 and 2 should include at least one PDF file. However, it is recognised that for some types of application no information is required in some parts of the dossier and in this situation the advice in section 8(a) above should be followed.

If more than one PDF is provided in any section, discrete studies or reports should not be split between PDF files unless necessary. If splitting is necessary it should be done at a sensible point to facilitate the review (i.e. do not split in the middle of a paragraph but rather between the text and the annexes for instance).

Naming

Any information that may help identify the contents of the file is encouraged to be included in the file name. The length of a path including file name, and extension should not exceed 230 characters.

The name of the files should be in English, descriptive of the section of the dossier, and, if pertinent, to the specific subsection. File names should be based on the naming convention used in the structure as defined in Tables 1 and 2 and have to include the part of the dossier where they are found in the name for example:

Part-1C2-Critical-Summary-Safety.PDF

Part-2E3-Identification-&-assay-of-excipient-components.PDF

Part-3A6-ERA.PDF.

If more than one PDF is included in a particular section then the files should also be numbered sequentially or given a descriptive name for example:

Part-3A6-ERA-Refs1-6.PDF.

If one document has to be split over more than one PDF because it is larger than 100 MB then the files should be numbered as “1ofx”, “2ofx” for example:

Part-3A3-Toxicology-rat-carcinogenicity-study-1of4.PDF

Where possible, applicants are strongly encouraged to use in subsequent submissions naming conventions consistent with the naming used in the initial submission.

Study reports and/or other literature will usually accompany the information provided in the dossier. These can be provided as individual PDF files or as a single PDF containing a number of studies. In general providing each study as a single PDF file is preferred. PDF files which are required in more than one section of the dossier need not be submitted more than once, although the file(s) can be submitted in each section in which they are required. If a file(s) is only to be submitted once but referenced a number of times then a simple cross-reference or a hyperlink to the section of the dossier where the files can be found is necessary.

Files should have the proper extension (e.g. PDF), and file names should not contain spaces or other characters which are known to give problems. In the case that filenames use codes to identify the document an index must be supplied in each directory of the folder structure. Files should have the proper extension (e.g. PDF), and file names should only be made up of characters 'a' to 'z' and '0' to '9' plus '-'. The file name should not contain any 'special' characters in particular the following characters are known to give problems.

' ' SPACE is not allowed (use Hyphen (minus) '-')
'.' FULL STOP is not allowed, except to separate files extension from rest of the file name.
':' COLON is not allowed
'/', '\ ' SLASH, BACKSLASH not allowed
'*' asterisk not allowed
'?' QUESTION MARK not allowed
'“' ”' QUOTATION MARK not allowed
'<' LESS THAN not allowed
'>' GREATER THAN not allowed
'|' 'PIPE' not allowed
'&' 'AMPERSAND' not allowed

9. Security

It is not permitted to apply password protection to either the media carrying the files or the files themselves. As with paper dossiers, authorities are obliged to have properly secured systems that guarantee the documentation is accessed only by authorized persons. Applicants have the right to get the assurance that the appropriate level of security is applied. It has to be recognised that some references taken from journals and other publications may not be able to be stripped of all security settings (e.g. preventing the copying of text from the article) without violating copyright rules. These files must then be exempt from a validation criterion regarding security settings.

10. Technical validation

An electronic submission will have to comply with the following criteria in order to be accepted as valid:

- Virus free
- No type of security on the CD/DVD or on individual files or folders (with exception noted in section 9)
- Follows the folder structure described in this guideline

- Follows the naming convention for folders described in this guideline (this should be observed for at least 95% of folder names)
- Files not >100 MB
- A GTOC file in the root directory and a TOC file in the folder for each part of the dossier
- Hyperlinks in the GTOC and TOC are functional (in the TOC this should be observed for 95% of hyperlinks)
- All documents should be in PDF 1.4 format (exceptions are: editable versions of the SPC and literature; the application form where an agency may require a later version)

The criteria listed above should be considered as a maximum set of criteria. Authorities should not enlarge the list as this will result in a non-unified approach to the validation.

11. Glossary

CD: "Compact Disc"; an optical disc that contains data accessible by a computer.

dpi: dot per inch; measure of printing resolution (number of individual dots of ink a printer or toner can produce within a linear one-inch (2.54 cm) space).

DVD: "Digital Versatile Disc" or "Digital Video Disc"; optical disc storage media format that can be used for data storage, with a capacity 8 times higher (single layer, single sided) than the CD.

eNTA: an electronic application prepared using a bespoke software package which contains an XML backbone and which follows the structure set out in Tables 1 and 2.

ERA: Environmental risk assessment

EUDRALINK: system designed to enable files to be sent securely over the Internet via a user-friendly Web interface, available to the EMEA, Member State Agencies, Industrial Pharmaceutical Companies, Members of Working Parties / Committees and Experts.

GTOC: General Table of Contents. The GTOC should be a complete index to the whole dossier.

ICH: International Conference on Harmonisation

ISO: International Organization for Standardization

MB: Megabyte; unit of information storage or computer storage

PDF: Portable Document Format

SmPC/SPC: Summary of Product Characteristic

TOC: Table of Contents. The TOC should be a complete index for that part of the dossier.

URA: User risk assessment

VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

VNeS: an electronic application prepared using standard software and which follows the structure set out in Tables 1 and 2.

TABLE 1
FOLDER STRUCTURE FOR AN ELECTRONIC APPLICATION FOR A
PHARMACEUTICAL PRODUCT

- 📁 root
 - 📁 additional-information
 - 📁 part-1-summary-of-the-dossier
 - 📁 1a-administrative-information
 - 📁 1b-spc-and-product-literature
 - 📁 1c-critical-summaries
 - 📁 1c1-quality
 - 📁 1c2-safety-and-residues
 - 📁 1c3-efficacy
 - 📁 part-2-quality-documentation
 - 📁 2a-qualitative-and-quantitative-particulars
 - 📁 2a1-qualitative-particulars
 - 📁 2a2-usual-terminology
 - 📁 2a3-quantitative-particulars
 - 📁 2a4-development-pharmaceutics
 - 📁 2b-description-of-the-manufacturing-method
 - 📁 2c-control-of-starting-materials
 - 📁 2c1-active substances
 - 📁 2c2-excipients
 - 📁 2c3-container-closure
 - 📁 2c4-substances-biological-origin
 - 📁 2d-control-tests-at intermediate-process-stages
 - 📁 2e-tests-on-the-finished-product
 - 📁 2e1-general-characteristics-of-the-finished-product
 - 📁 2e2-identification-and-assay-of-active-substance(s)
 - 📁 2e3-identification-and-assay-of-excipient-components
 - 📁 2e4-safety-tests
 - 📁 2f-stability-tests
 - 📁 2f1-active-substances(s)
 - 📁 2f2-finished-product
 - 📁 2g-other-information
 - 📁 part-3-safety-and-residues-tests
 - 📁 3a-safety-tests
 - 📁 3a1-precise-identification-of-product-and-active
 - 📁 3a2-pharmacology
 - 📁 3a3-toxicology
 - 📁 3a4-other-requirements
 - 📁 3a5-ura
 - 📁 3a6-era
 - 📁 3b-residue-tests
 - 📁 3b1-identification-of-product
 - 📁 3b2-metabolism-and-residue-kinetics
 - 📁 3b3-residue-analytical-method
 - 📁 part-4-preclinical-and-clinical-trials
 - 📁 4a-preclinical-requirements
 - 📁 4a1-pharmacology
 - 📁 4a2-resistance
 - 📁 4a3-target-animal-tolerance
 - 📁 4b-clinical-requirements
 - 📁 4b1-clinical-trials

TABLE 2
FOLDER STRUCTURE FOR AN ELECTRONIC APPLICATION FOR AN
IMMUNOLOGICAL PRODUCT

- 📁 root
 - 📁 additional-information
 - 📁 part-1-summary-of-the-dossier
 - 📁 1a-administrative-information
 - 📁 1b-spc-and-product-literature
 - 📁 1c-critical-summaries
 - 📁 1c1-quality
 - 📁 1c2-safety
 - 📁 1c3-efficacy
 - 📁 part-2-quality-documentation
 - 📁 2a-qualitative-and-quantitative-particulars
 - 📁 2a1-qualitative-particulars
 - 📁 2a2-usual-terminology
 - 📁 2a3-quantitative-particulars
 - 📁 2a4-product-development
 - 📁 2b-description-of-manufacturing-method
 - 📁 2c-production-and-control-of-starting-materials
 - 📁 2c1-starting-materials-listed-in-pharmacopoeias
 - 📁 2c2-starting-materials-not-listed-in-a-pharmacopoeia
 - 📁 2d-control-tests-during-the-manufacturing-process
 - 📁 2e-control-tests-on-the-finished-product
 - 📁 2e1-general-characteristics
 - 📁 2e2-identification-of-active-substance(s)
 - 📁 2e3-batch-titre-or-potency
 - 📁 2e4-identification-&-assay-of-adjuvants
 - 📁 2e5-identification-&-assay-of-excipient-components
 - 📁 2e6-safety-tests
 - 📁 2e7-sterility-&-purity-test
 - 📁 2e8-residual-humidity
 - 📁 2e9-inactivation
 - 📁 2f-batch-to-batch-consistency
 - 📁 2g-stability-tests
 - 📁 2h-other-information
 - 📁 part-3-safety-documentation
 - 📁 3a-general-requirements
 - 📁 3b-laboratory-tests
 - 📁 3b1-safety-of-one-dose
 - 📁 3b2-safety-of-an-overdose
 - 📁 3b3-safety-of-the-repeated-administration-of-one-dose
 - 📁 3b4-examination-of-reproductive-performance
 - 📁 3b5-examination-of-immunological-functions
 - 📁 3b6-special-requirements-for-live-vaccines
 - 📁 3b7-ura
 - 📁 3b8-study-of-residues
 - 📁 3b9-interactions
 - 📁 3c-field-studies
 - 📁 3d-era
 - 📁 3e-assessment-of-products-containing-or-consisting-of-gmos
 - 📁 part-4-efficacy-documentation
 - 📁 4a-general-requirements
 - 📁 4b-laboratory-trials
 - 📁 4c-field-trials