12 March 2015
EMA/CVMP/VICH/758781/2013-Corr.[1]
Committee for Medicinal Products for Veterinary Use (CVMP)

VICH GL53: Electronic exchange of documents: electronic file format

Adoption by CVMP for release for consultation	**13 February 2014**
Transmission to interested parties	21 February 2014
End of consultation (deadline for comments)	20 July 2014
Agreed by VICH Steering Committee	February 2015
Adoption by CVMP	12 March 2015
Date for coming into effect	February 2016

[1] On page 8 reference has been made to 'section 0' – this has been corrected to 'section 2.1'

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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

VICH GL53 (EFF) – ELECTRONIC FILE FORMAT
Corrected
September 2015
For implementation at Step 7

ELECTRONIC EXCHANGE OF DOCUMENTS: ELECTRONIC FILE FORMAT

Adopted at Step 7 of the VICH Process by the VICH Steering Committee in February 2015 for implementation by February 2016.

This Guideline has been developed by the appropriate VICH Expert Working Group and has been subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA.

Secretariat : c/o IFAH, rue Defacqz, 1 - B - 1000 Bruxelles (Belgium) - Tel. +32 2 543 75 72, Fax +32 2 543 75 85
e-mail: sec@vichsec.org – Website: www.vichsec.org

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Objective of the guideline

The electronic exchange of regulatory documents concerning veterinary medicinal products between industry and regulatory authorities is commonplace. Global harmonisation of the specifications for the electronic file format of documents is seen as a fundamental starting point to realising the potential benefits.

1.2 Scope

The scope of this guideline is to cover the electronic file format specifications for individual documents and collections of multiple related documents that do not need subsequent modification during the regulatory procedure and are utilised for electronic exchange between industry and regulatory authorities in the context of regulatory approval of veterinary medicinal products. It applies to communication or data exchanged as documents in the context of all regulatory procedures where regulatory authorities accept electronic transfer of such documents. This may include but is not limited to applications for initial marketing authorisations, related pre-submission or post-authorisation procedures, applications for maximum residue limits, clinical trial applications, drug / active substance master files or requests for regulatory or scientific advice, etc. (depending on a regional legislative situation).

This guideline provides different options and specific recommendations related to the electronic format of exchanged files. Following the recommendations outlined in this guideline will help ensuring that electronic files are suitable and appropriate for regulatory review but will also involve complying with specific IT requirements.

Working documents that need to be maintained in their native file format for further editing (e.g. Microsoft (MS) Word), such as proposed label texts, are outside the scope of this guideline.

An implementation period of one year after adoption of the guideline is recommended. However, it may be voluntary applied earlier where electronic exchange of documents within the scope of this guideline is already accepted by regulatory authorities at the time of adoption of this document.

For business processes that are still paper-based, implementation of this guideline may be suspended by regulatory authorities until electronic exchange can be accepted.

Specific recommendations may apply to country-/region-specific documents, for example, application forms or facsimile copies of labels for use in the country or region.

The guideline is addressed as a guidance document to industry; however, voluntary acceptance of the principles of this guideline for documents created by regulatory authorities for exchange with industry is also encouraged.

1.3 Basic principles

A standard interchange file format for documents that do not need to be modified or extracted into databases should fulfil the following basic principles:

- can be generated from other electronic source formats or digitized from paper;
- is designed for viewing and/or printing;

- allows the use of a document viewer whose specifications are in the public domain;
- relies on major international standards like those of the International Organization for Standardization (ISO);
- is both device and resolution independent;
- retains the content and the layout of the original document;
- remains useable and accessible long-term;
- preserves the visual appearance of file content over time;
- supports regulatory review needs, including searchable text;
- builds on a format that already has broad acceptance among industry and regulatory authorities;
- is a cost-efficient solution for the veterinary sector.

2 PORTABLE DOCUMENT FORMAT (PDF) FILE FORMAT

The following sections address:

- File format specifications for single files (section 2.1) and additional specifications for hyperlinked files (section 2.2). These specifications may be used as basis for establishing pass / fail criteria, i.e. rejection of incompliant files.
- Best practices, which significantly enhance the review process, but which should not be a ground for rejection of files (section 2.3).

When following the single file specifications detailed in section 2.1, two options are available:

- Option 1 describes PDF/A-compliant files. This is the easiest way to comply with these file format specifications. Simply saving a single document as PDF/A file using any PDF/A-compliant software does automatically cover most file format specifications.
- Option 2 describes a minimum set of specifications for PDF files without formal PDF/A compliance. This option may for example be preferable in a transition phase, during which submitting applicants are not yet ready to produce fully PDF/A-compliant files.

Publications should where possible follow the format specifications of option 1 or option 2. As they are public source documents and different restrictions for long-term storage appear to be acceptable, these files are exempted from the application of criteria beyond PDF version and file integrity.

2.1 Single-file transfer

Option 1: PDF/A-conforming files:

A standard interchange format for electronic transfer of documents that follows the principles as set out in section 1.3 is PDF/A, which restricts PDF in a way that it is optimized for exchange and long-term reproducibility of the content.

PDF files that conform to [ISO-19005-1:2005], [ISO-19005-2:2011] or [ISO-19005-3:2012] are accepted for all types of electronic exchange of non-editable documents between industry and regulatory authorities. Note however that the use of embedded files or PDF portfolios / PDF packages, though they may conform to the PDF/A ISO standard, is not adequate for regulatory review (see table below and section 2.3 for further details).

Minimum PDF/A conformance level, i.e. Level B conformance (PDF/A-1b, PDF/A-2b or PDF/A-3b) is sufficient and is also recommended as this level is the easiest to comply with. Compliance with higher levels of PDF/A conformance such as Level A or Level U is not necessary but such files will be accepted as well.

The specification is available from the ISO web site: http://www.iso.org/.

It is important to note that the PDF/A ISO standard also specifies that the application (PDF reader) that is reading and processing PDF files complying with a specified conformance level, should comply with all relevant specifications as detailed in [ISO-19005] to ensure that the document is correctly displayed or printed.

Note that the PDF/A specification alone cannot ensure that the visual appearance of the content accurately reflects the original source material used to create the conforming file.

Applicants therefore should control the process used to create a conforming file to ensure that a PDF/A file is an accurate visual representation of the original source document. Potential issues to be observed are incorrect or missing characters caused by inappropriate font substitution, or a negative impact on quality of images due to inappropriate down sampling or poor – e.g. maximum lossy – compression. Applicants should also be aware that the quality of elements like graphics is already determined within the authoring software (e.g. the word processing software used).

Option 2: Minimum specifications for non-PDF/A conforming files:

Where a document does not conform to the PDF/A ISO standard, applicants should observe the following minimum specifications. These should be followed to ensure that it is adequate for regulatory review, to increase long-term sustainability and to ease a potential conversion process to an archive format (i.e. PDF/A) and therefore also make reference to some important PDF/A specifications.

Feature	**Specification**	**Comment**
PDF Version	Files have been created and saved as PDF 1.4, 1.5, 1.6, or PDF 1.7.	Based on [ISO 32000-1:2008] Document management - Portable document format -- Part 1: PDF 1.7. Use of PDF Extension Levels to version 1.7 does not lead to rejection / invalidation of files.
Security settings	No type of security on individual files.	Password protection preventing access to the document or restricting permissions, e.g. to prevent printing or the copying of text, is not allowed.

Feature	Specification	Comment
		Documents which may not be able to be stripped of all security settings are exempted. This includes references taken from journals and other publications or PDF forms provided by regulatory authorities. To provide a secure mechanism for exchange of confidential information between applicants and regulatory authorities the use of appropriate tools like secure web portals or secure gateway-to-gateway communication is recommended. PDF files in such cases should not be password-protected for reasons of security. Password-protected, encrypted ZIP or PDF files should be used only in case of unprotected transfer (e.g. via email) and if agreed between applicant and receiving authority. Note that encrypted PDF files cannot be converted to PDF/A. Please consult guidance of national/regional authorities concerning available methods for file transfer.
Prohibited PDF features	PDF files do not contain:	
	• JavaScript and executable file launches	Region-specific documents like electronic application forms with JavaScript functionality provided by regulatory authorities are exempted.
	• External content references (Everything needed to render or print a PDF file must be contained within the file.)	Note that external hyperlinks to other PDF documents if used in a multi-file submission (see section 2.2) or to web pages are in conformance with the PDF/A ISO standard.
	• Dynamic content which can include audio, video, 3D content or other special effects and animations	
	• Attachments (embedded files)	Embedded files are not adequate for regulatory review as they can be easily overlooked during compilation / review of documents and may complicate technical

Feature	Specification	Comment
		validation.
Font embedding	Every font used for visible text should be embedded within the PDF file.	The PDF/A ISO standard requires embedding of fonts used for rendition of visible text only. Thus invisible fonts used in scanned documents for creating searchable text by an Optical Character Recognition (OCR) routine may be embedded but are exempted from the embedding requirement of the ISO standard. The PDF/A ISO standard requires only embedding of the subset of characters actually used in a given font. Embedding complete fonts needlessly increases the size of the PDF file. All embedded fonts must also be legally embeddable, i.e. licence agreements must allow unlimited embedding into the PDF file, either fully or as a subset, for the purpose of printing or viewing the document. Subsetting and use of commonly used fonts is recommended from a copyright perspective.
File integrity	Files must not be corrupted.	For technical validation a check may be achieved by opening a file in a PDF reader which is compliant to [ISO 32000-1:2008]. If the file opens without error, the PDF file is considered to be conformant. Note that this method may not detect all possible errors within a file. To avoid delays in the review process the applicant should carefully check file integrity before transfer, again preferably using a standard-compliant reader. Browsing the complete document page by page will assure that the full content is accessible. In combination with above technical PDF check by regulatory authorities, this simple manual check effectively assures that a reviewer can fully access all received documents.

2.2 Multiple-file transfer

In case of transfers of multiple documents some regulatory authorities recommend or even request the use of inter-document hyperlinks to other PDF files to improve the efficiency of navigating through such submissions.

Note that inter-document hyperlinks may become non-functional when files are maintained within a regulatory authority's document management system which does not support inter-document hyperlinks. Therefore the applicant should consult relevant guidance from national/regional authorities to avoid investing resources into hyperlinks when the applicant has to submit only to regulatory authorities that are not able to benefit from such improved navigation.

Note that external hyperlinks to other documents in a submission in principle are in conformance with the PDF/A ISO standard. Where PDF/A is used, authors however should observe that specific hyperlink actions are forbidden in [ISO-19005] (see section 2.3 for further details), and reviewers may need to configure ISO compliant readers to make external hyperlinks actionable.

When such inter-document hyperlinks are requested, additionally to section 2.1, the following specifications apply:

Feature	Specification	Comment
Inter-document hyperlinks or bookmarks	Destination file path	To maintain the functionality of hyperlinks, inter-document hyperlinks or bookmarks should refer to other PDF files by using relative file paths and all files should remain in the same relative location in a folder structure after hyperlinking. To allow reading on certain devices, using non-Windows operating systems, hyperlinks and bookmarks should be configured as specified in [ISO 32000-1:2008]. Specifically the paths should use forward slashes. Consult the PDF specifications as in [ISO 32000-1:2008], section 7.11.2.3 for further detail. Please note, that some PDF tools display the path for the link with backslashes, though the link in the PDF file is fully conforming to these ISO specifications. Open the PDF file with a simple text editor or validate with an appropriate tool to confirm conformance in case of doubt.

2.3 Best-practice recommendations

There are additional features that are considered good practice for preparation of regulatory relevant documents. PDF files that are not in conformance with such practice will not be rejected by regulatory authorities however applicants are reminded that following these best practices will significantly enhance the efficiency of any review process.

Feature	Recommendation
File size	File size of a single file should be limited to 100 MB.
Fonts	It is recommended to use fonts that are used by most text processors like Arial, Courier and Times New Roman or other fonts with similar level of usage. No customised fonts should be used. Use an adequate font size that ensures legibility. Use black font colour for normal text. Blue font may be used for hypertext links. For languages not based on Latin Characters like Japanese an appropriate multi-byte character font supporting Unicode should be used.
Graphics / Images	When creating PDF files containing graphics or images, use lossless compression until the final rendition is created. Alternatively use the most limited / highest-quality lossy compression that does not compromise visual quality. For files containing colour images / colour photos consider a colour model based on RGB. As sRGB (standard RGB colour space as specified in [International Electrotechnical Commission (IEC) 61966-2-1]) is the native colour space for usual source applications, operating systems and most digital cameras and scanners, this avoids conversion to another colour model and potential negative impact on image fidelity.
Hyperlinks + bookmarks (general recommendations)	Intra-document hyperlinks and bookmarks should be used to assist the reviewers in navigating through the content of a submitted document. Where recommended by regulatory authorities, inter-document hyperlinks and bookmarks should be used to assist the reviewers in navigating through the content of a multi-file submission. Text hyperlinks should be visibly distinct from other text (e.g. blue text may be used). When creating bookmarks and hyperlinks, the magnification setting should be set to “Inherit Zoom”. Where bookmarks are used the initial view of the PDF file should be set as “Bookmarks Panel and Page”.

Feature	Recommendation
	Hyperlinks to web pages may be used if they are active and the destination is given as a valid web address, also known as uniform resource locator (URL). All URL's should be displayed as a fully qualified URL such as: http://www.vichsec.org/. As URLs may change after preparation of a document, hyperlinks to web pages should however not be used for any content relevant for the assessment of the transferred file(s). In such cases a PDF rendition of the page(s) should be created and submitted as a separate document.
Hyperlinks from PDF to PDF files	When setting hyperlinks between PDF documents, in the PDF writer the link action to jump to a page view of another ("remote") PDF file should be chosen. Technically this is known as a "Remote Go-To Action". An action to open another file should not be chosen. Technical background: Because JavaScript and executable file launches are forbidden in [ISO-19005], a hyperlink cannot be made by such means. Such hyperlinks may also be lost during PDF/A creation. Instead, hyperlinks should be provided as specified in [ISO 32000-1:2008], section 12.6.4.3 "Remote Go-To Actions" (GoToR). In case of doubt, use of correct hyperlinks parameters can be confirmed with the help of a simple text editor.
Hyperlinks to other destination file formats	In exceptional cases, hyperlinks to open a file of a different file format may be provided (e.g. to graphic files as specified in section 3 or to an MS Word file). When setting hyperlinks to non-PDF documents, in the PDF writer the link action to open a web page should be chosen to enter the Uniform Resource Identifier (URI) of the destination file, i.e. the full name and where applicable the destination file path. Technically this is known as an "URI Action". Note that in addition the recommendations of section 2.2 for file paths apply. Technical background: Note that hyperlinks based on a "Launch Action" (see [ISO 32000-1:2008], section 12.6.4.5) are not allowed in [ISO-19005]. Such hyperlinks may also be lost during PDF/A creation. Therefore hyperlinks to other file formats should use the URI action as specified in [ISO 32000-1:2008], section 12.6.4.7 "URI Actions".
Page numbering	Pages within an individual file should be numbered. The initial page of the source document and PDF document should be numbered page 1.
Page orientation	Pages should be properly oriented. For example, you should set the page orientation of landscape pages to landscape prior to saving the PDF document in final form to ensure correct page presentation.
Page view settings	Use "default" initial page view settings for page layout and magnification.

Feature	Recommendation
PDF portfolio / PDF package (portable collections)	The use of PDF portfolios is in conformance with the PDF/A ISO standard. Nevertheless use of such PDF collections should be avoided as its functionality may rely on presence of other software and thus may cause issues during the review process.
Print area	Ensure that sufficient page margins and readability are maintained in printouts, regardless of whether ISO 216:2007 A4 (210 x 297 mm) or a Letter format (8.5 inches by 11 inches) sheet of paper is used for printing. This may be achieved either by a smaller print area using only the overlapping area of both formats (allowing printing without resizing), or by appropriate formatting of the document to ensure its readability is not adversely affected by resizing to the other format, e.g. by using sufficiently large font sizes. Files used for local/regional submission only (including mock-ups) are exempted.
Resolution of scanned elements	If scanning is unavoidable the following scanning parameters should be used: Scanning of text documents at a resolution of not less than 300 dots per inch (dpi) will normally balance legibility and file size. Higher resolution may be required for scanned graphics. When saving scanned documents, lossy compression should only be used with caution as it might compromise legibility. For example, visible artefacts may be created around complex high-contrast image areas like text. Therefore such images are unsuitable for lossy compression, as opposed to continuous-tone photographic images.
Source format	PDF files should be created (rendered) directly from their electronic source documents, except where the applicant has no access to the electronic source document.

In addition, care should be taken in the settings defined for the PDF writer used to ensure that no device-specific options are embedded in the PDF file (i.e. for a specific physical output device like a printer) as the file format should be device-independent.

3 OTHER FILE FORMATS

The default file format for narrative documents that need no subsequent editing is PDF. This recommendation applies likewise to graphic documents. However in exceptional cases when appropriate for review purposes, the following file formats may also be used:

- Joint Photographic Experts Group (JPEG),
- Scalable Vector Graphics (SVG),
- Graphics Interchange Format (GIF) and
- Tagged Image File Format (TIFF) [ISO 12234-2:2001].

4 REFERENCES

[IEC 61966-2-1:1999] Multimedia systems and equipment – Colour measurement and management – Part 2-1: Colour management – Default RGB colour space – sRGB.

[ISO 12234-2:2001] Electronic still-picture imaging -- Removable memory -- Part 2: TIFF/EP image data format.

[ISO 19005-1:2005] Document management -- Electronic document file format for long-term preservation -- Part 1: Use of PDF 1.4 (PDF/A-1).

[ISO 19005-2:2011] Document management -- Electronic document file format for long-term preservation -- Part 2: Use of ISO 32000-1 (PDF/A-2).

[ISO 19005-3:2012] Document management -- Electronic document file format for long-term preservation -- Part 3: Use of ISO 32000-1 with support for embedded files (PDF/A-3).

[ISO 32000-1:2008] Document management -- Portable document format -- Part 1: PDF 1.7.[2]

[2] An ISO approved copy of the ISO 32000-1 standards document is available as a free PDF on the Adobe Web site (http://wwwimages.adobe.com/www.adobe.com/content/dam/Adobe/en/devnet/pdf/pdfs/PDF32000_2008.pdf). It is not an official ISO document but the technical content is identical and page and section numbers are preserved.