VICH/12/056
FINAL

PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

VICH draft Guideline 53: Electronic exchange of documents Electronic File Format

VICH EWG: ELECTRONIC FILE FORMAT (EFF)

Comment n°	Name - Country
1	IFAH-Europe
2	FDA
3	AHI
4	EGGVP
5	Office National de Sécurité Sanitaire des Produits Alimentaires – ONSSA, Morocco
6	EMA
7	Australian Pesticides and Veterinary Medicines Authority (APVMA)

Editorial notes

- Line numbers regarding comments from EU (Stakeholder 1) relate to EMA document EMA/CVMP/VICH/758781/2013.

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Discussion of comments

GENERAL COMMENTS – OVERVIEW

Comment N°	Comment received	Outcome of consideration
1	IFAH-Europe welcomes the opportunity to comment on this guideline. Please find our comments hereunder.	N/A
2	All mandatory/prescriptive/standard setting language will need to be removed as this is a guidance, not a regulation	Partly agreed. Guidance text has been reworded for clarification.
4	EGGVP acknowledges and supports the efforts of VICH towards harmonized file format requirements for the electronic exchange of regulatory documents at global level, and therefore welcomes this proposal. Although it is clear that the scope of this guideline excludes documents that need further editing, EGGVP believes that it would certainly be beneficial if these (labelling texts, SPCs…) were included in order to optimize the benefits both for applicants and regulators. Some basic recommendation in this area would be to avoid marking pdf documents in written (which are often illegible) during the exchange, but to submit those in word format with track changes. Furthermore, the marketing authorizations could preferably be exchanged in bilingual (local language + English) versions as a general rule. That would make the exchange much more efficient, in particular when the applicant is not familiar with the local language. EGGVP would appreciate if VICH could agree with these principles and therefore proceed with the scope enlargement to cover editable documents too; or alternatively can consider the publication of a separate guideline to cover this type of documents' exchange.	Comment noted. Indeed working documents that need to be maintained in their native file format (e.g. MS Word) for further editing during an interim period, such as proposed label texts, have been determined to be out of the scope of this guideline. This decision has been taken as such files are usually for regional or national use only and from a perspective of long-term sustainability they are less critical. Therefore currently no need to extend the scope of this VICH guideline is seen. Procedural aspects like languages to be used or use of tracked changes are out of scope of this guidance. The scope of this guideline is to give file format recommendations The use of MS Office is broadly accepted for such purposes without known issues, however it should also be noted that MS Word is no open standard but a proprietary file format.

Comment N°	Comment received	Outcome of consideration
5	Cette directive est un document intéressant. Elle est relativement synthétique. Elle permet l'harmonisation des documents échangés entre les industriels pharmaceutiques et l'autorité compétente ainsi que les pratiques d'échange. En ce qui concerne la structuration, nous proposons l'ordre suivant: • Généralités; • Bonnes pratiques ; • Exigences et paramètres d'échange des fichiers simples; • Exigences et paramètres d'échange des fichiers multiples.	Thank you very much for the comments! As regards the structure of the document, it does currently start with introductory and scope statements followed by general principles as indicated in your proposal. For the following chapter however we think it will be appropriate to start with the most important recommendations first, as these will assure acceptance by the receiving agency. Following best practices in addition to these key recommendations will significantly enhance the efficiency of any review process, but best practices cannot be a reason for non-acceptance of files. Based on this reasoning we prefer to keep the current order of sections, starting with the most important parameters first. For a better understanding of this rational an explanatory text is added at the beginning of section 2: "The following sections address: • File format recommendations for single files (section 2.1) and additional recommendations for hyperlinked files (section 2.2). These recommendations 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 never should be a ground for rejection of files (section 2.3).

Comment N°	Comment received	Outcome of consideration
		When following the single file recommendations detailed in section 2.1, two options are available: • Option 1 recommends PDF/A-compliant files. This is the easiest way to comply with these file format recommendations. Simply saving a single document as PDF/A file using any PDF/A-compliant software does automatically cover most file format recommendations. • Option 2 describes a minimum set of recommendations 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-conforming files.”
6	After the implementation period of one year, consider to start the sentence with (instead of having it at the end)‘However, it may be voluntarily applied earlier,’ Replace ‘regulators’ by ‘regulatory authorities’ and replace ‘guidance’ by ‘guideline’.	Thank you for the suggestions, which were carried out.

Comment N°	Comment received	Outcome of consideration
7	We are required by law to keep data supporting submissions for 50 years after registrations ceases if **no** major or significant health or environmental issues have arisen. If there are major or significant issues the data is retained forever. Overall the draft requirements are good; they support Australian government archiving specifications specifically – • PDF/A conforming files (pg4) • Graphics and images based on RGB (pg9) • Resolution of scanned elements not less than 300 dpi (pg11) We are concerned about documents with hyperlinks to webpages (pg9) as over time we may not be able to access these pages. Also file size (pg8) limited to 100MB – our web Portal at this stage will accept single files up to 25MB only. Files above 25 MB must be submitted on USB /CD. I don't see this as necessitating a change in the draft GL. Other comments – • Security Settings (pg. 5) - not accepting password protected files is good; our Portal also does not accept password protected files. • Prohibited PDF features (pg6) – the prohibitions support our current capability – • JavaScript and executable file launches – our electronic document and records management system (EDRMS) does not accommodate executable file launches without customisation, as we have done for CADDY submissions. • External content references and Attachments (embedded files) – these should work from within our EDRMS • Dynamic content – these files can be large and resource intensive.	Thank you for the comments. Most of the comments either support the Guideline or explain the local context. In both cases, there are no changes requested to the text of the Guideline.

Comment N°	Comment received	Outcome of consideration
	• Multiple-file transfer (pg7) "Note that inter-document hyperlinks may become non-functional when files are maintained within an agency's document management system." We agree – inter-document hyperlinks may not work in our EDRMS. For this reason, files must be readily searchable and indexed. • Inter-document hyperlinks or bookmarks (pg8) – as above; these may not work in our EDRMS, and files must be readily searchable and indexed.	
2	<u>FDA response to comments received during public consultation in the US:</u> <u>General Comment 1</u> With respect to electronic clinical trial data capture, most data is collected via web-page based EDC systems and stored in a server database once submitted. If the intent of this document is to address these submissions as well as application documents, then we recommend allowing HTML format in addition to PDF. HTML (e.g., "save-as" on a web-page) is a suitable format that meets the recommendations of Section 1.3, and has many advantages over PDF formats. Advantages include linking of pages, resizing in browsers, rendering directly from their corresponding source data, human-readable (non-proprietary), and better match to the web forms. In addition, the limitations on size given the large resulting size of PDFs make PDFs labor-intensive to package for submission, losing much of the linkage and additional information such as drop-down entries. Since the 1.2 Scope section of the guidance includes applications for "clinical trial applications", is the intention for the guidance to address the new drug application document itself, or is the intention to address the EDC data capture as well? If the latter is included, there seems to be a disconnect with other CVM guidance regarding e-Submitter, which along with XML format, also includes PDF document standards for clinical data submission. Does this guidance harmonize with the e-Submitter guidance?	

Comment N°	Comment received	Outcome of consideration
	FDA's Response to Comment 1 CVM will not accept HTML as part of any submission. The remainder of the comment is outside the scope of the document. The intent of the document is not to discuss file formats for submitting data files that will be manipulated during the review process No changes to GL53 are required in response to this comment. General Comment 2 I recommend that in addition to the use of the PDF standard and sub-standards (e.g. PDF/A) for interoperability of documents for human readability, there are additional conformance statements regarding document metadata using existing features of the PDF standard. This is to satisfy separation of provenance information from document content for human readability as well as computational discoverability and indexing. The language should also include the use of title, author, subject, keyword, date created/modified and application metadata conformant to the "PDF Info Dictionary" and in conformance with terms from the Dublin Core Metadata Vocabulary (e.g. dc:title, dc:subject). I also recommend that document file names require a less proscriptive, but best practices guidance, so they are effectively self-describing and reasonably unique so that document topic, provenance (author/organization) and date be included. The date should also be internationalized and unambiguous with logically consistence progressive sequence of YYYYMMMD or DDDMMYYYY, not MMDDYYYY, etc. FDA's Response to Comment 2 CVM recognizes the potential value added by the inclusion of metadata when creating PDF documents. However, CVM is not prepared at this time to make recommendations to which data elements should be included in this document. The inclusion of metadata recommendations could be included as part of a future revision to the document. No changes to GL53 are required in response to this comment.	Concerning Comment 2: Meta data may indeed have added value but not necessarily need to be directly included in the PDF file. Agreed to have at this time no changes to GL53 in response to this comment. At next revision of the guidance text, the suggestion might be re-considered.

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION 2 PDF FILE FORMAT RECOMMENDATIONS/2.1 Single-file transfer / Option 1: PDF/A-conforming files:			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	3	Editorial corrections only: "Note however that the use of embedded files or PDF portfolios / PDF packages, though ~~it~~ they may conform…" And further down the text: "It is important to note that the PDF/A standard also specifies that ~~also~~ the application (PDF reader)~~,~~"	Accepted.
	1	Compliance with higher levels of PDF/A conformance such as Level A is not necessary but such files will be accepted as well." ISO 19005-2:2011 defines two higher conformance levels (Level A and U). As both should be fully acceptable it is proposed to list for reasons of clarity both levels in this context. Proposed change: Please modify lines 128-129 to read: "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."	Level U conformance (PDF/A-2u) represents full Level B conformance with the additional requirement that all text in the document have Unicode equivalents (i.e. maps character codes for at least all referenced glyphs to Unicode values). Basically this improves usability of the file and such files would be fully acceptable. The proposed change can therefore be accepted.
	3	For clarification please provide an example for "poor compression", e.g. "maximum lossy".	Accepted.

SECTION 2 PDF FILE FORMAT RECOMMENDATIONS/2.1 Single-file transfer / Option 2: Minimum restrictions for non-PDF/A conforming files			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	1	For implementation of VICH file format requirements publications should be exempted from the application of the pass/fail criteria "font embedding" and "prohibited PDF features". For publications there may be fonts used in the file that the applicant does not have and thus cannot embed. In addition, according to the draft VICH guideline so far with good reason publications are exempted from the criterion "no security settings". As a logical consequence this means for those files that are password protected that the applicant cannot change such files, neither related to font embedding nor to any other prohibited PDF feature e.g. file attachments. In this case there are two options left, either exemption from such pass/fail criteria or (always as last resort) scanning. The latter does not appear to be the preferable option. Proposed change: In conclusion, though publications should where possible follow all criteria, they are public source documents and different restrictions for long-term storage appear to be acceptable. It is therefore proposed to exempt these files from the application of P/F criteria beyond being PDF 1.4 to PDF1.7 and not being corrupt (similar as in the current VNeeS criteria in the EU).	Accepted. An explanatory text is added at the beginning of section: "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."
	3	In the table under "File integrity" add clarification that "the applicant should carefully check file integrity before transfer, preferably using a standard-compliant reader."	Accepted. To effectively assure that files are not corrupt and can be used properly in the review process, both checks on the regulators side and pre-checks done by the industry should to be done with software that follows the ISO standard rules.

SECTION 2 PDF FILE FORMAT RECOMMENDATIONS/2.2 Multiple-file transfer			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	4	The draft Guideline states that "regulatory agencies recommend or even request the use of inter-document hyperlinks" and then "Note that inter-document hyperlinks may become non-functional" and "they will be useless for navigation and therefore may not be recommended". These statements are contradictory and may lead to confusion. Clarification if hyperlinks are recommended or not may be appropriate.	Partly agreed. The two statements describe two separate scenarios and therefore are not contradictory. Where agencies recommend or request the use of inter-document hyperlinks, their own IT systems obviously should be fully compatible with their use. Where agencies are not asking for hyperlinks, the latter cannot be assumed by default. In such cases hyperlinks would not be recommended by the specific agency concerned, though in principal they can be very helpful for navigation. The effort of hyperlinking a submission in such cases would not be justified, if this submission is provided only to a single agency <u>not</u> being prepared to use hyperlinks in their own systems. In case of doubt therefore applicants should consult relevant guidance of national/regional authorities. To avoid misunderstanding the text of this paragraph has been amended.
	3	<u>Editorial corrections only:</u> Amend 1st sentence as follows: "to improve ~~navigation~~ <u>the</u> efficiency <u>of navigating</u> through such submissions…."	Accepted.

SECTION 2 PDF FILE FORMAT RECOMMENDATIONS/2.2 Multiple-file transfer			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	5	*Transfer de fichiers multiple:* Certaines spécifications figurant dans le tableau sont trop techniques, ce qui peut décourager les candidats d'adopter cette ligne directrice	It is agreed that the necessary level of technical detail is always a balancing act between necessary accuracy needed for IT implementation and readability for non-IT executives. The specific points mentioned in this table, i.e. relative file path and use of forward slashes in such paths, often are default settings in off-the-shelf software and may then be no issue in daily praxis. In addition they can be easily verified with a simple text editor or tested with an appropriate tool (e.g. the VNeeS checker validation tool in the EU) to confirm conformance in case of doubt. It will be considered whether a Q&A document supporting an implementation phase can be helpful.
	3	In the table (feature "Inter-document hyperlinks or bookmarks") please add the word "PDF" in the last sentence: "Open the PDF file with a simple text editor or validate with an appropriate tool to confirm conformance in case of doubt."	Accepted.

SECTION 2 PDF FILE FORMAT RECOMMENDATIONS2.3 Best-practice recommendations			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	5	Nécessité d'adopter des normes ISO relatives aux exigences informatiques par les autorités des pays concernés..	It is correct that formal adoption of ISO standards need to be based on decisions by the regulatory authorities or governments of the countries concerned as ISO is a non-governmental organization which has no power to enforce the implementation of the standards it develops. In the current guideline ISO standards are referred to because major international standards are a very suitable basis for voluntary mutual acceptance of electronic files following a specified format. This does not necessarily depend on prior legal adoption of the ISO norms themselves in all of the countries concerned.
	3	Table (Item “Fonts”). Remove brackets. “Use black font colour for normal text. Blue font may be used for hypertext links.”	Accepted.
	5	Table (Item “Print area”) Faire deux phrases plus explicites pour la compréhension du commentaire: Les surfaces d'impression pour les pages doivent correspondre à la norme ISO 216:2007 A4 (210 x 297 mm). Les feuilles de papier du format lettre (8,5 pouces par Il pouces) doivent permettre d'assurer des marges suffisantes et une bonne lisibilité du texte.	Partly accepted. It is agreed that splitting the sentence will increase readability. The meaning of this recommendation is however to ensure that sufficient page margins and readability of the document are maintained in printouts, regardless of whether A4 or a Letter format sheets of paper are used for printing. To achieve that either the print area has to be reduced or the document has to be formatted appropriately (e.g. sufficiently large font size)

SECTION 2 PDF FILE FORMAT RECOMMENDATIONS2.3 Best-practice recommendations			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
			to avoid negative impact on readability in case of resizing. Based on this and similar questions it is however agreed that the wording needs to be improved and slightly more detailed for better understanding: "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."

SECTION 3 OTHER FILE FORMATS			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	3	Editorial correction only: "However in exceptional cases, when appropriate for review purposes, ~~also~~ the following file formats may <u>also</u> "be used:	Accepted..

SECTION 4 REFERENCES			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
	3	Editorial correction only: Delete first hyphen in references for PDF/A-1 and 2: [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).	Accepted..