eAF becomes mandatory for all procedures – what to consider by applicants

Webinar for the usage of an eAF at applicants level

Presented by: Georg Neuwirther, Klaus Menges and Kristiina Puusaari

Agenda

1. **Overview and Status of Implementation**
   Speaker: Georg Neuwirther (AGES, chair eAF MG)

2. **Usage of an eAF at applicants level**
   Speaker: Kristiina Puusaari (EMA) and Klaus Menges (BfArM)

3. **Questions and Discussion**

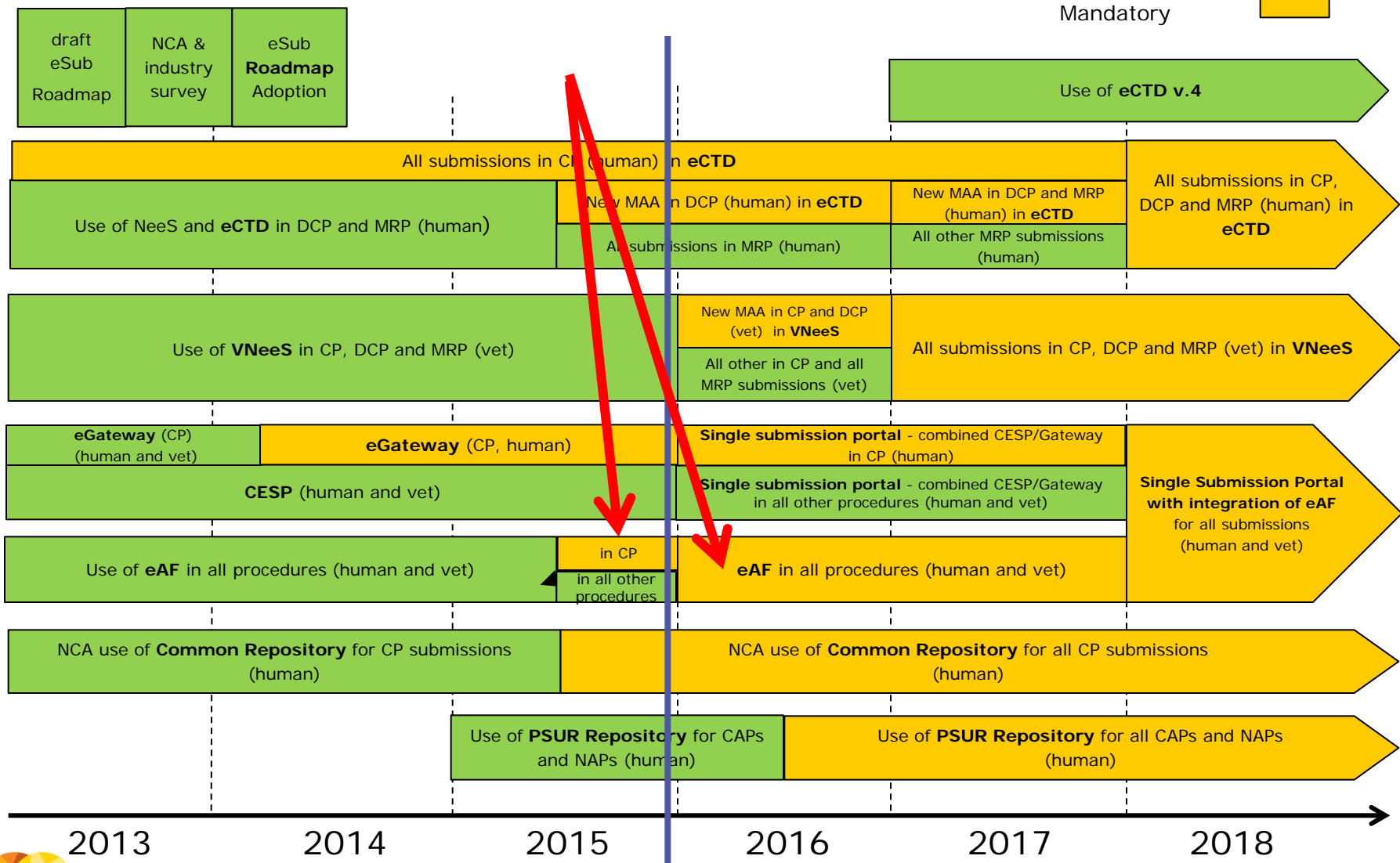# OVERVIEW AND STATUS OF IMPLEMENTATION

eAF Maintenance Group (eAF MG)

- Group of business and IT-experts from NCAs, EMA and Industry

- eAF MG is in charge of implementing the eAF according to the eSubmission Roadmap

- Evolution: 1. word AF -> 2. eAF -> 3. Single Submission Portal

- Please contact us via eaf@ema.europa.eu for any questions!

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Background eSubmission Roadmap

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(reflecting final adopted version 1.0 dated 07/11/14)

Ongoing/optional
Mandatory

draft eSub Roadmap	NCA & industry survey	eSub **Roadmap** Adoption

Use of **eCTD v.4**

All submissions in CP (human) in **eCTD**

Use of NeeS and **eCTD** in DCP and MRP (human)	New MAA in DCP (human) in **eCTD**	New MAA in DCP and MRP (human) in **eCTD**	All submissions in CP, DCP and MRP (human) in **eCTD**
	All submissions in MRP (human)	All other MRP submissions (human)	

Use of **VNeeS** in CP, DCP and MRP (vet)	New MAA in CP and DCP (vet) in **VNeeS**	All submissions in CP, DCP and MRP (vet) in **VNeeS**
	All other in CP and all MRP submissions (vet)	

eGateway (CP) (human and vet)	eGateway (CP, human)	**Single submission portal** - combined CESP/Gateway in CP (human)	**Single Submission Portal** with integration of eAF for all submissions (human and vet)
CESP (human and vet)		**Single submission portal** - combined CESP/Gateway in all other procedures (human and vet)	

Use of **eAF** in all procedures (human and vet)	in CP	**eAF** in all procedures (human and vet)	
	in all other procedures		

NCA use of **Common Repository** for CP submissions (human)	NCA use of **Common Repository** for all CP submissions (human)

Use of **PSUR Repository** for CAPs and NAPs (human)	Use of **PSUR Repository** for all CAPs and NAPs (human)

2013   2014   2015   2016   2017   2018
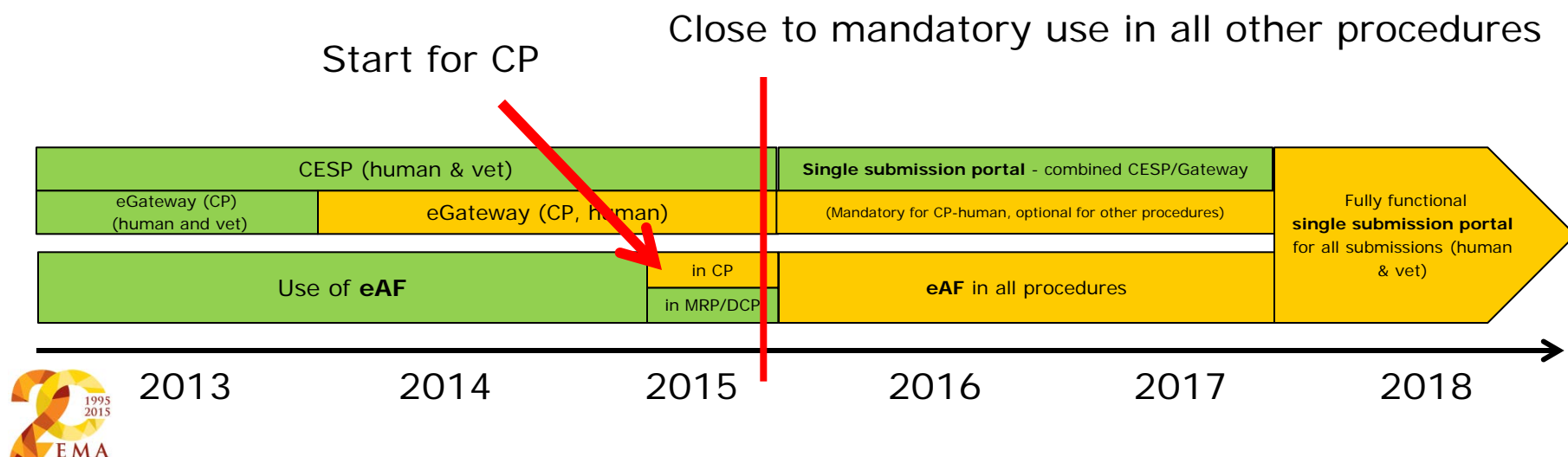
eSubmission Roadmap Timelines

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Successful start of compulsory usage of the eAF for Centralised Procedures (all types, human&veterinary) on the 1st of July 2015

- Current figures: only <1% of CP submissions do not contain eAF-compliant application forms! Non-compliant submissions are rejected and resubmission is requested.

- Please ensure to use the correct eAF-version
- Please do not print and scan the eAF as a replace of the electronic version!
  This will delay the application!

Start for CP

Close to mandatory use in all other procedures

CESP (human & vet)	Single submission portal - combined CESP/Gateway	Fully functional **single submission portal** for all submissions (human & vet)

eGateway (CP) (human and vet) | eGateway (CP, human) | (Mandatory for CP-human, optional for other procedures)

Use of **eAF** | in CP / in MRP/DCP | **eAF** in all procedures

2013   2014   2015   2016   2017   2018

Option 1 - link to eAF webpage from Eudralex page

Notice to Applicants (European Commission)

- http://ec.europa.eu/health/documents/eudralex/vol-2

- http://ec.europa.eu/health/documents/eudralex/vol-6/index_en.htm

Note: From January 2016 the Word-AF will be removed from the Eudralex website!

Option 2

eSubmission Homepage (EMA)

http://esubmission.ema.europa.eu/eaf/index.html

Release Plan

published here: http://esubmission.ema.europa.eu/eaf/index.html

Excerpt of Release Plan (status 30.11.2015)
Please check website for updates!

Milestone	Date
Publication of eAF version 1.19.0.1	30/11/15
eAF v01.19.0.1 replaces all previous versions (v1.19, v1.18,..)	11/01/16 Older versions will not be accepted after this date for new submissions
Publication of eAF version 1.20	15/04/16

Current detail plan for eAF v.1.20

eAF v.1.19.0.1	**in use**	Accepted (Would only be possible if filled in and downloaded before 01.05.)	Accepted in case of validation errors only (Possible only if version 1.19 was used in the invalid submission)

eAF v.1.20	develop-ment	**in use**	

01.05.2016
v1.19 withdrawn
from website

15.04.2016
v1.20 published
on website and usage
strongly recommended

01.06.2016

timeline
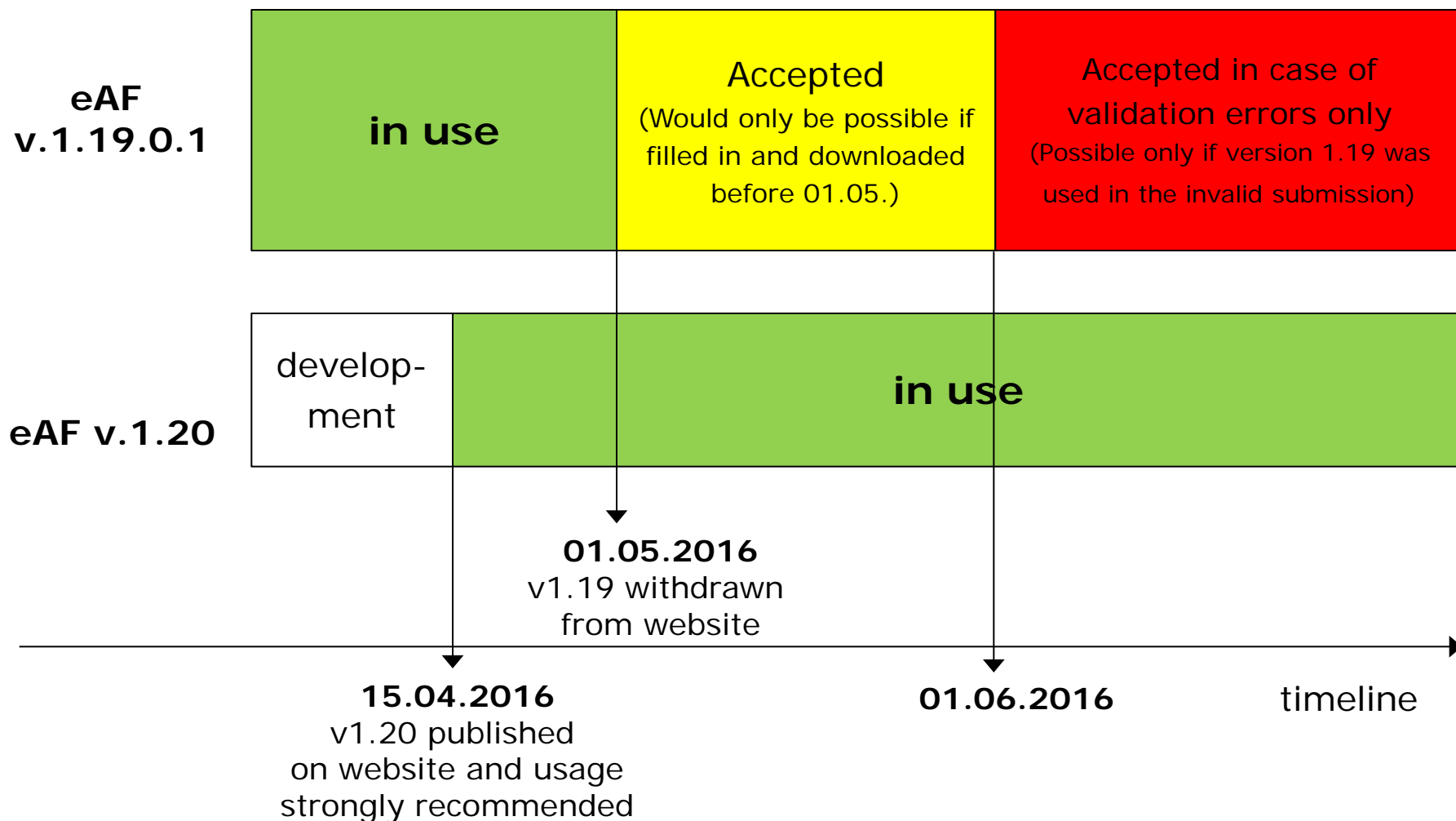
Why guidance documents – eAF will contain the same data as before?

yes, and …

- eAFs provide less free text sections, defines more data structure and makes use of controlled terms (EUTCT)
- Provides features which were not possible with WORD

Change process for applicants and agencies!

— Guidance Documents

Regulatory

User Guide for the electronic application form for a marketing authorisation (Human) **New**

User Guide for the electronic application form for a marketing authorisation (Veterinary) **New**

Technical

Technical guidance Human and Vet (19/10/2015) **New**

Q & A

User Guidance Human & Vet	Questions and Answers (19/10/2015) **New**
Benchmark response times	eAF performance

What to do at applicant level (key steps)?

- Check IT infrastructure (Adobe reader version 10 or above)

- Check internet-connectivity to EUTCT (e.g. for search for substances)

- Update internal guidelines and offer internal trainings

- Organise templates for AFs
  - Usage of XML-files, "Save-AS"

- Be prepared for updates of eAFs
  - Check eAF website for Release Plan and Release Notes
  - User Acceptance Tests will be announced

- Evaluate automated data import into eAF (from industry IT systems)
  - A data exchange standard is published on the eAF-website

HANDLING THE ᴇAF

- Scope of the eAFs
- eAF support structure
- Impact of mandatory use
- Receipt and validation
- Look and feel
- Navigation
- Locking the form and signatures
- Form validation
- Controlled terminology and Term Request Process for EUTCT
- Workarounds
- Known defects
- How to submit in VNeeS, Nees and eCTD, examples in human areas how do it best (file naming)
- XML Export and Import
- Q&A

Note: There is no principal difference for initial applications, variations or renewals

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- The eAFs are replacing the Notice to Applicants (NTA) Initial Human and Veterinary MAA forms, Variation form and the Renewal application forms

- The eAFs must be used for all Human and Veterinary submissions for Centralised Procedure and MRP/DCP and National Procedures

- The Homeopathic form and all other EMA or NCA specific forms, for example the pre-submission form or the 61.3 notification form remain in their existing formats – they are currently out of the scope of the eAF project

Effective support for applicants & NCAs/EMA will be a key success factor during the implementation phase of mandatory use of the eAF for all EU procedures!

Why will support be needed?

- Technical change from Word to PDF format

- eAF structure cannot be changed by the applicant like Word forms

- Majority of free text fields have been replaced by controlled vocabularies – terms are selected from EUTCT-catalogues – if terms are no available they should be requested through MDMS new term request process

- Paper forms were isolated documents with no direct IT-integration into the business process (e.g. for automatic data import). Now eAF data will be used directly in IT-systems reducing manual workload and human error

- Technical questions, comments, change requests – send your questions to eAF@ema.europa.eu

- Procedural questions

  - CP – eAF@ema.europa.eu

  - MRP/DCP/NP– if questions are received to eAF@ema.europa.eu and are very specific to a particular NCA/application the applicant is advised to contact the RMS/relevant NCA using the normal channels for queries to the NCAs.

  - Mixed queries containing both technical and procedural queries should be sent directly to RMS/NCA – RMS/NCA may forward the reply to eAF@ema.europa.eu and EMA will complete response with the technical details and will reply directly to the applicant with NCA in copy

  - Mixed queries containing both technical and procedural queries received by EMA – EMA will reply to the user providing response on the technical issue and will direct the applicant to RMS/NCA for the procedure aspects

eAF- Support Structure

(no big differences to the AS-IS-situation)
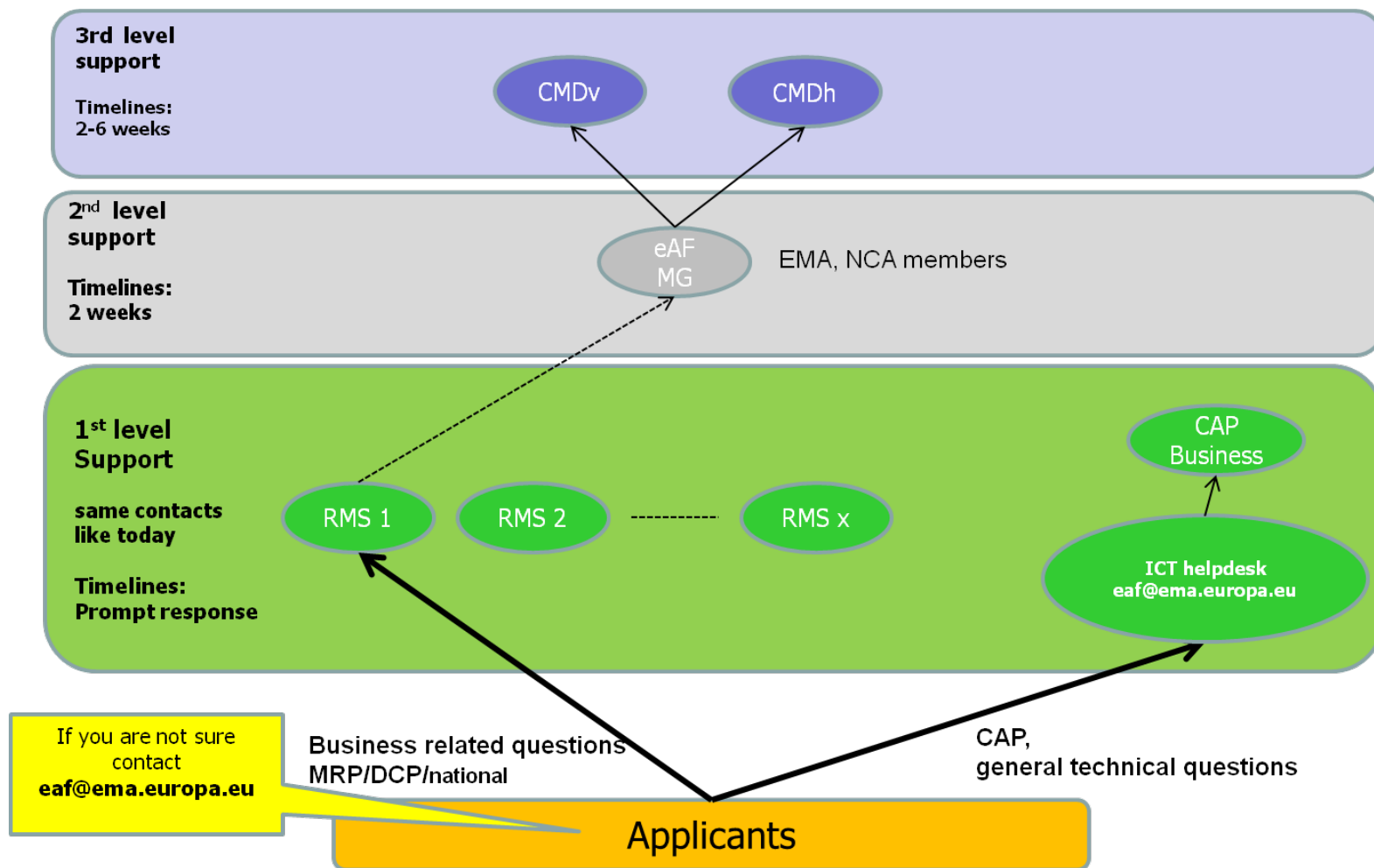
Preparation

- There is no further transitional period regarding the mandatory usage – the forms are available from the eAF website

- The eAFs should be submitted as 'real' eAFs – meaning that they are kept in electronic format and are submitted with the xml. Forms that have been printed and scanned as PDF lose all their intelligent features and become flat PDFs. These do not allow import/export of xml data into receiving systems

- The eAFs are mandatory also for submissions where the product lifecycle is paper based – i.e. eAFs must be used also for paper submissions (NTA form is replaced by eAF which can be printed if required)

- The mandatory use of the eAFs does not change any existing wet signature requirements by the NCAs – only the form changes – i.e. instead of the word or pdf version of the AF available in the NTA Eudralex website the only forms available are the PDF eAFs

Preparation

- Completing the form is based on controlled terminologies and is less flexible than using the paper forms. You should check at an early stage whether all terms needed are available via the form. If terms are not available through the form you should request new terms using the defined new term request process.

- Applicants should note that it will take slightly longer to open to the eAF PDFs than the paper application forms. This is due to the build in business rules and the controlled terminologies in the forms. Approximate opening times have been gathered and are published on the eAF website on a document called eAF performance. EMA is continuously working hard to improve the performance of the forms.

eAF – Impact of mandatory use

Form versions

- The Notice to Applicants (NTA) application forms are updated regularly and to ensure that the eAF corresponds with the latest NTA forms new versions of the eAFs are launched. In majority of the eAF versions include changes implemented in NTA forms. Alongside these changes, additional usability improvements are provided based on prioritised change requests. NTA announces a date from when onwards the new version must be used. For releases without any NTA changes, the mandatory use date is decided together with the network at the eAF maintenance group (MG)

- Version 1.19 of the eAFs is reflecting changes in the NTA initial MAA form and additionally, number of change requests have been implemented in all four forms. All implemented change requests are listed on the eAF release notes available on the eAF webpage.

- V 0.20 will bring further bug fixes and usability improvements based on change requests prioritised by the eAF MG (consisting of NCAs and industry).
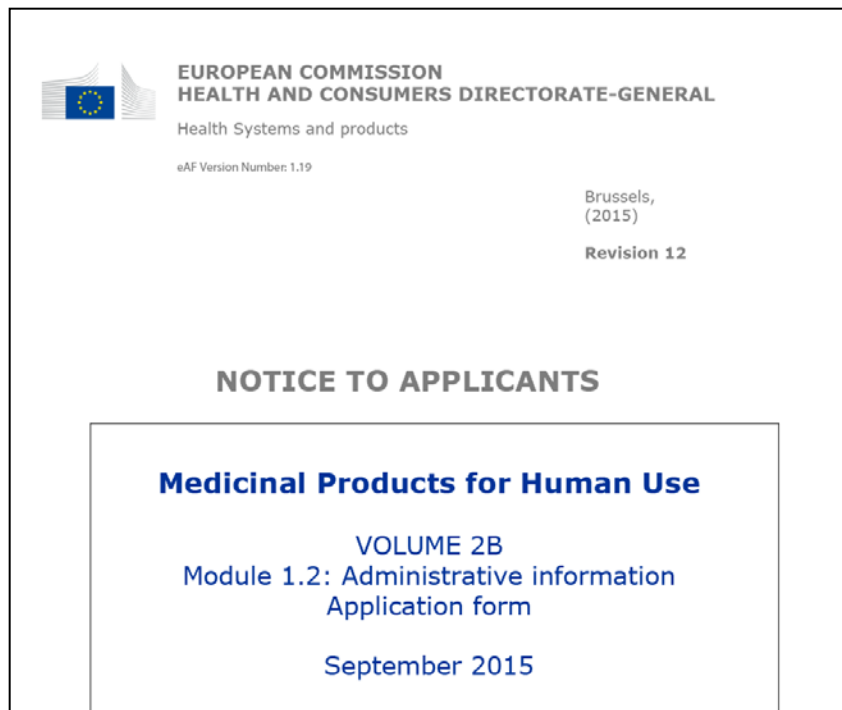
- All applications submitted after 1 January 2016 should be submitted in eAF format – it is the applicants responsibility to provide the application using the correct version of the eAFs

- Paper forms are only accepted for ongoing procedures after the mandatory use starts – there is no need to convert from NTA paper form to an eAF in the middle of the procedure!

- As usual previous versions of the forms are accepted for ongoing procedures – there is no need to update the form version in the middle of the procedure

- As with any application form – the eAFs should be provided as a part of the submission package i.e. for eCTD submissions the eAF should be included inside the eCTD structure in Module 1 folder 1.2. Similarly for NeeS or VNeeS submissions, the eAF should be provided as a part of the submission

- The eAFs should not be sent as a separate email or CESP submissions

- The eAF should be provided in PDF format within the submission.

- The applicants should not provide the xml extraction along with the submission data as it would lead to a need to check that the xml and the PDF are identical.

- The receiving NCAs will extract the xml where necessary for their business processes

- A known issue with the Fast Web View not being compatible with eAFs – eCTD and NeeS validation tools will give Best Practice error which should be ignored.

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- All applications submitted after 1 January 2016 should be prepared in eAF format

- You can recognise the eAFs easily as they look different from the NTA paper forms, see example below of :

  – the Initial H-MAA:

eAF

Paper form

eAF – Look and feel

– the Initial V-MAA:

eAF

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

eAF Version Number: 1.19

Brussels, 01.06.2015

Revision 7.4

NOTICE TO APPLICANTS

Medicinal Products for Veterinary Use

VOLUME 6B
Presentation and content of the dossier-Part 1
Summary of the dossier Part 1A
Application form

June 2015

Note: The error in the European Commission header for the initial V-MAA eAF has been noticed and will be updated in the next release of the eAF.

Paper form

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE GENERAL

Health Systems and products

Brussels, 01.06.2015

Revision 7.4

NOTICE TO APPLICANTS

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VOLUME 6B
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June 2015

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– <u>the Variation application</u>:

eAF   **Paper form**

– <u>the renewal application form</u>:

eAF   **Paper form**

Navigation before and after locking the form

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unlocked

locked

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2. **PRODUCTS CONCERNED BY THIS APPLICATION[7]**
3. **TYPES OF CHANGE(S)**

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DECLARATION OF THE APPLICANT

SIGNATURE

NOTES

FORM VALIDATION

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DECLARATION AND SIGNATURE

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FORM VALIDATION

Click to advance to named section.

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DECLARATION AND SIGNATURE

NOTES

FORM VALIDATION

1995
2015
EMA

eAF – form validation

- All eAFs contain built in business validation based on complex validation rules – if you identify incorrect business rules please report to eAF@ema.europa.eu to raise a change request

- Ideally, all validation errors are solved before finalising and locking the form –it's very important to save the unlocked forms before closing them in case there are any validation issues and updated form is requested – it is not possible to change already locked forms and in case no unlocked version has been saved you might have to refill the whole form in order to make changes to respond to the validation comments

- Occasionally it is not possible to solve all validation comments and once the forms are locked the form will display the number of 'form validation errors' at the very end of the form – however it is not possible to see to which sections these validation errors refer to. Validation errors in the form can, in most cases, be ignored as these often refer to sections for which a separate annex has been provided.

FORM VALIDATION

Validation Errors: 0

- The form validation is not a technical eCTD or NeeS/VNeeS validation

- Leaving validation errors in the form does not affect eCTD or NeeS/VNeeS validation - the purpose of this validation is simply to guide you to fill in the form correctly and to fill in mandatory fields of the forms

- In many cases, form validation errors do not lead business validation errors

- Form that doesn't have any form validation errors might still be invalidated during the business validation step – it's important not to confuse form validation with business content validation!

- If a new version of the forms has become available / entered into force between the receipt of a new (initial, variation or renewal) application and request for supplementary information (validation comments) - the applicant **does not** need to change the form version

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- After finalising data entry you will need to lock the form before submitting it to the authorities
- Save the un-locked form in advance, you may need to change data at a later point in time
- Navigate to section 'Signature'
- The tool tip describes the actions required.
- Select an image from file system
- Before the form is locked a validation process is running and will indicate all missing values
- This process cannot be stopped
- Once the process ended all fields are displayed in grey, the validation error sum will be displayed at the far end of the form

Function	
Address 1	Kurt-Georg-Kiesinger-Allee 3
Address 2	
Postcode	53175
Country	Germany
Telephone	+49 228 207 3458
Telefax	
E-mail	klaus.menges@bfarm.de
Date	

In process once the signature image has been added and saving the file was confirmed

Signatory   Validating Form - Please Wait

This form was authorised following company policies by Dr. K. Menges, Senior Reg. Affairs Manager of BfArM with authorisation to sign. The signature is in file.

Note: please attach letter of authorisation for communication/signing on behalf of the applicant in (Annex 5.4)

Note: if fees have been paid, attach proof of payment in (Annex 5.1) - see information on fee payments on EMA/C

FORM VALIDATION

Validation Errors: 0

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- Once the form has been saved and is locked the presentation changes to grey
- The image could be an image of a real signature as well

On behalf of the applicant

Copy contact details from previous section

Title

First name* Klaus

Surname Menges

Function

Address 1 Kurt-Georg-Kiesinger-Allee 3

Address 2

Postcode 53175

Country Germany

Telephone +49 228 207 3458

Telefax

E-mail klaus.menges@bfarm.de

Date

Signatory

* ☐ Note: please attach letter of authorisation for communication/signing on behalf of the applicant in (Annex 5.4)

** ☐ Note: if fees have been paid, attach proof of payment (Annex 5.1) see information on fee payments on EMA/CMDh website.

eAF – controlled terminology

- The dropdown lists or selections from catalogues include terms according to standardised nomenclatures and quality standards for medicinal substances and products of EDQM or the EUTCT system

- In case of a missing term please use the eAF Term Request Form. Once completed, you will need to submit your form via email to mdms@ema.europa.eu

- A provisional term may be added to the list within 5 working days; however, please note that there is a possibility that the term might not be approved and ultimately added to the list for future use. For further guidance please refer to http://esubmission.ema.europa.eu/eaf/5_eAF%20Term%20Request%20Process.ppt

- In case NCAs identify an inappropriate term used the applicant must correct it and should ask for a provisional term according to the defined process

- All controlled terminology lists used in the eAF can be found from EUTCT

- Initial testing shows that it is possible to copy content selected from dropdown menus in v.1.19 – this might depend on the version of Adobe you have available

eAF Term Request Process

In case MAH/NCA will ask for new terms
→ EMA provides a standardised request procedure available on the eAF website

| (day 0) MAH fills in request form and emails request to mdms@ema.europa.eu | *Term request evaluation process* | (+5 day) MDMS Service desk informs MAH of term to be used |
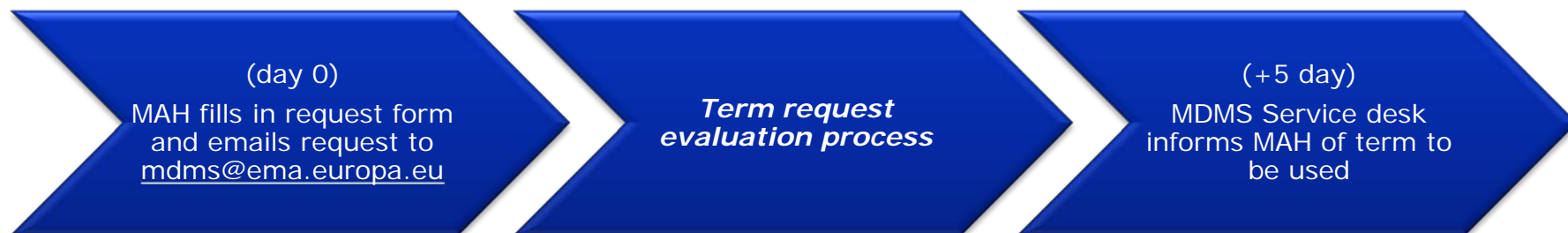
* In the term request form there are detailed instructions on what information is required to apply for changes in each list.
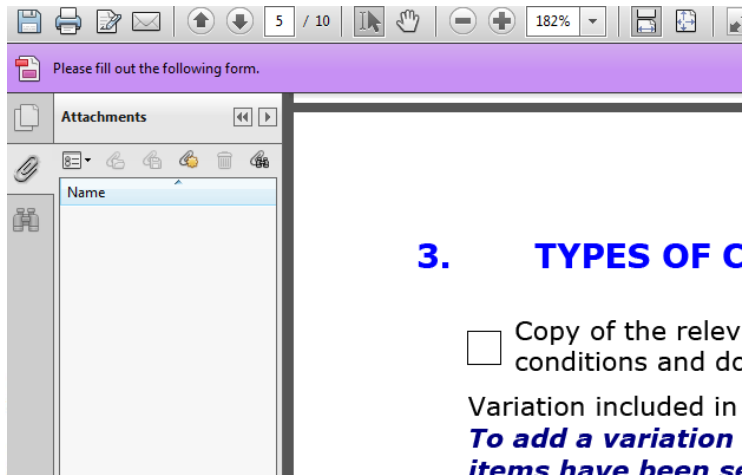
eAF Term Request Process – 5 days SLA

eAF – workaround solutions
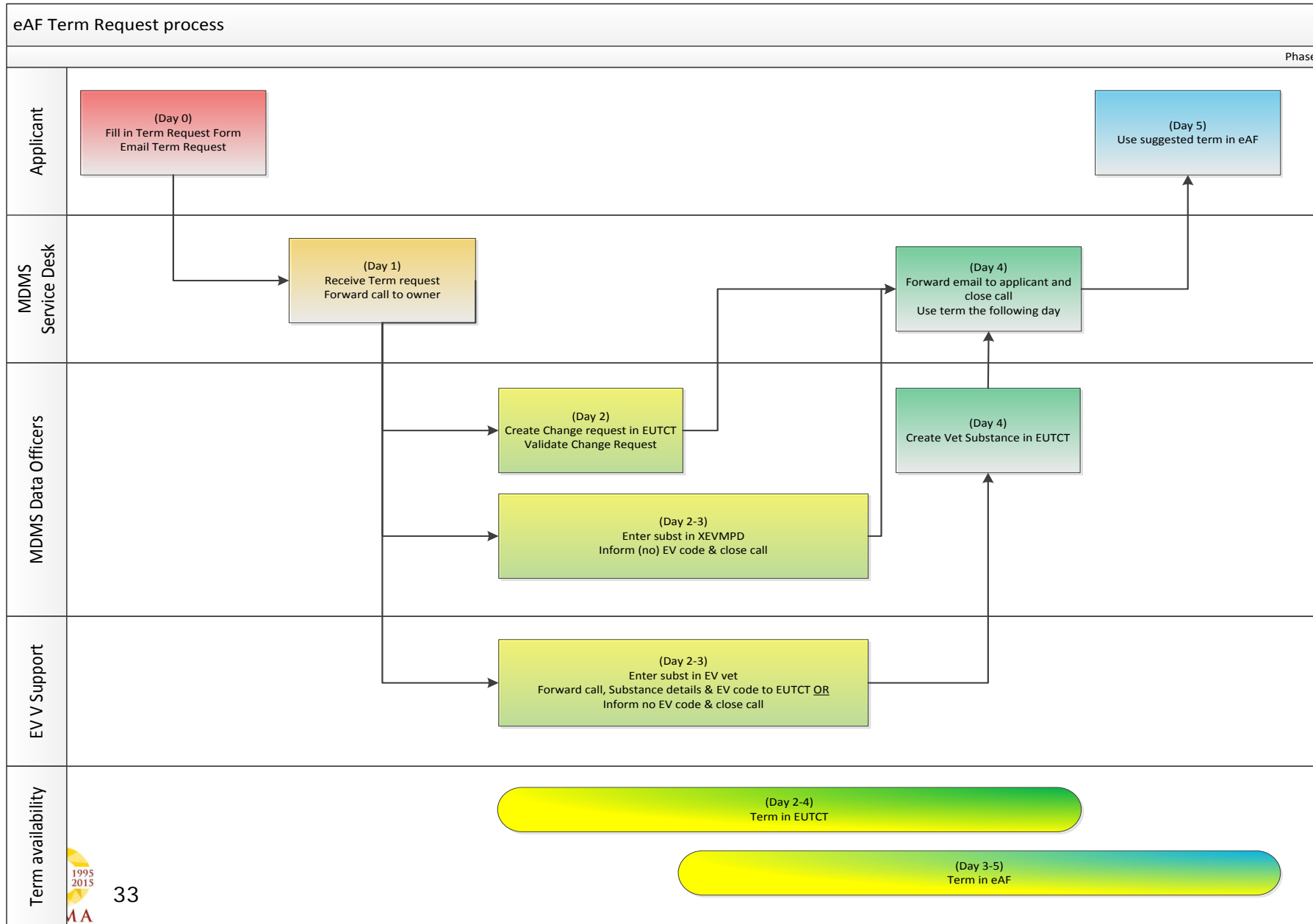
- The most commonly used workaround solution is an addition of an annex to the form as the relevant section cannot be filled as required in the eAF - these are not the annexes as referred to e.g. in section 5 of the initial forms

- The annex must be included as a separate, **clearly named** document in the same folder (e.g. 1.2 in EU M1) where the application form is provided! We recommend that the annex is named as per the section of the form that is provided in the annex.

- The standard PDF functionality of adding an annex using the paperclip function must not be used as the annexed documents will not be visible when viewed via eCTD review tool (e.g. EURS)

eAF – workaround solutions

- For MRP/DCP the renewal form might contain multiple product names all entered in the same single row as the current version of the form does not allow duplication of the 'Invented name' field.

Is the product currently marketed?   ◉ Yes   ○ No

In which Member States[2]?   ⓘ

| Member state | Germany | ▼ | + | - |
| Member state | Finland | ▼ | + | - |
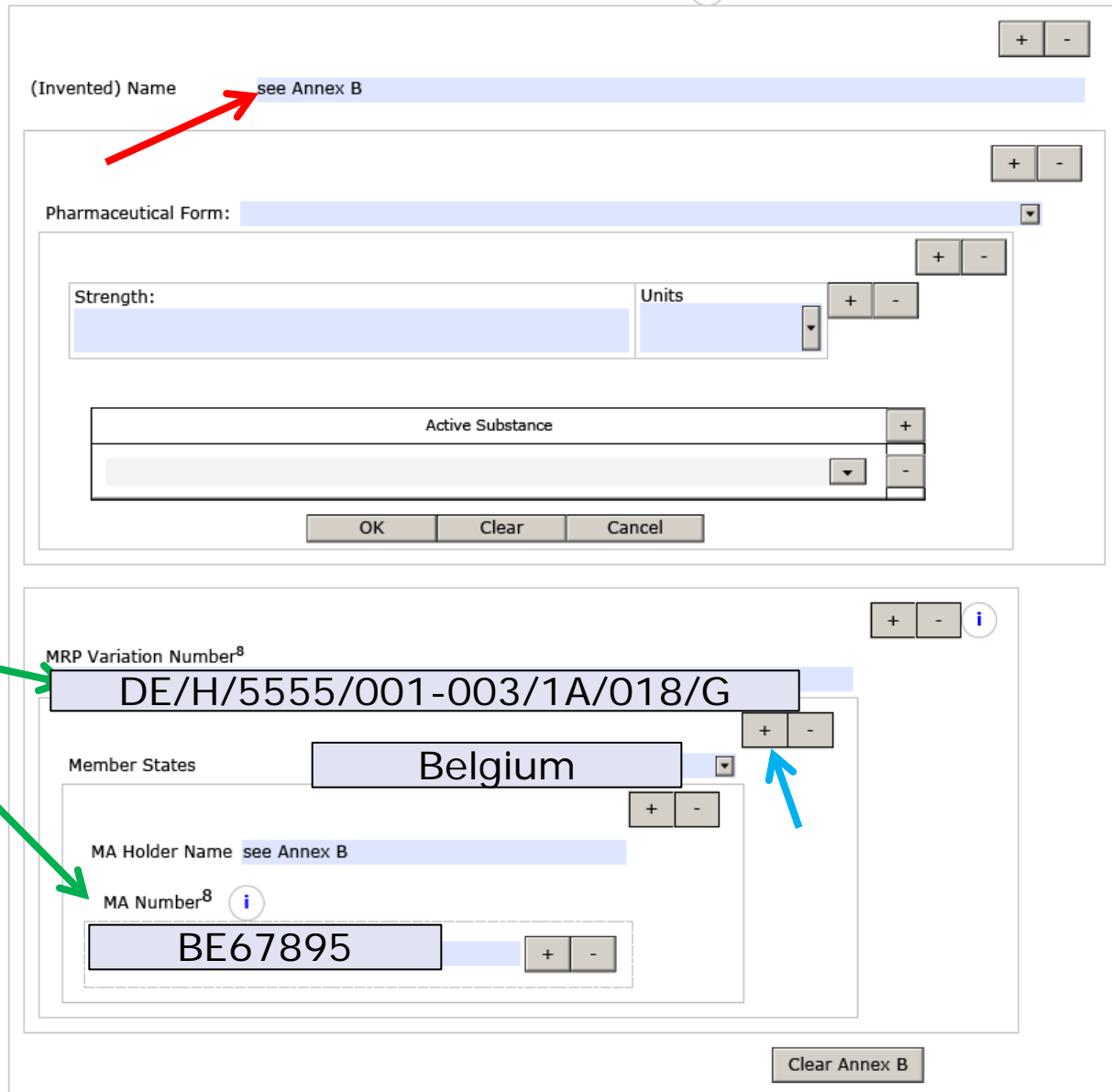
Invented Name   DE: Product A, FI: Product B, BE: Product C

- This is an existing change request based on feedback from NCAs that this is a field that is duplicated in the paper forms.

eAF – workaround solutions

- For MRP/DCP the variation form will cover multiple product names by using the Annex B option.
- You need to enter the high level number in section 1 or

  DE/H/5555/001-003/1A/018/G

  in case of worksharing, where to include the product specific variation number

  AT/H/xxxx/001G

- You should also enter the MRP number and the national authorisation number before using the Annex B option to allow a proper identification of the product out of the XML data set.
- Repeat the lower section as needed.

2. **PRODUCTS CONCERNED BY THIS APPLICATION**[7] (i)

(Invented) Name   see Annex B

Pharmaceutical Form:

Strength: Units

Active Substance

OK   Clear   Cancel

MRP Variation Number[8]

DE/H/5555/001-003/1A/018/G

Member States   Belgium
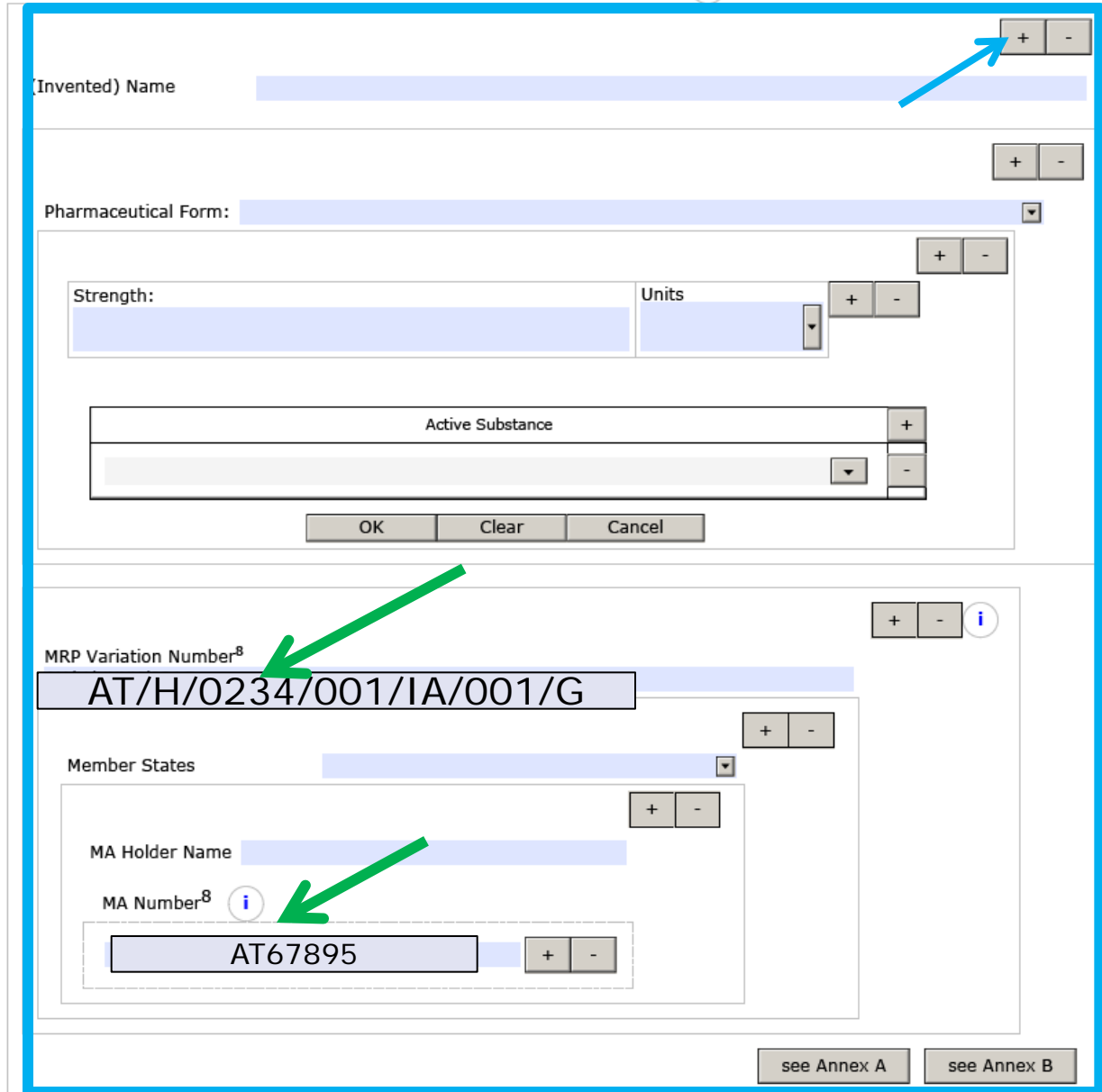
MA Holder Name   see Annex B

MA Number[8] (i)

BE67895

Clear Annex B

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eAF – workaround solutions

- Duplicating the entire section should only be used in case products are concerned which differ in regard to pharmaceutical form and active ingredients.

- If different product names need to be covered the previous workaround is easier to handle.

- Entering the correct MRP number is again essential to allow a proper identification of the product out of the XML data set.

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eAF – workaround solutions

- Detailed instructions how to use workaround solutions is available in the eAF Q&A document and the eAF Technical Guidance documents – both are published on the eAF webpage – if you need more advice contact eAF@ema.europa.eu

- If you have a question that is not responded to in the guidance documents send your question to eAF@ema.europa.eu. Most commonly asked questions will be added in to the Q&A document and in the eAF Technical Guidance document during the next update of these documents

- The forms have been built so that they contain build in business rules, guiding you to fill in the forms the correct way and this might in some sections compromise flexibility, however, the forms remain flexible and there are multiple different ways to fill in several sections depending on each specific application. EMA directs applicants to NCAs/RMS when there are questions on how to fill in certain parts of the forms for MRP/DCP/NP applications to ensure there are no content validation issues

eAF – workaround solutions

- Advice from EMA and NCAs for the applicants for workaround solutions is to always mention in the application cover letter that a workaround solution has been used to avoid any business validation issues. There is no need to mention the workaround for addition of the salt/hydrate form as this is not displayed as a workaround for NCAs.

- The current version of the forms has some known defects and issues for which an updated 'known defects and workaround solutions document' will be made available on the eSubmission website.

- Some of the known defects in the forms released on 9th November 2015 were severe and an emergency hotfix was released on Monday 30th November 2015 – the date from when the v1.19 will replace v1.18 has been postponed until 11th January 2016 – the date of the mandatory use of the eAF has not been postponed!

- During this transitional period, until 11th of January 2016, both versions v1.18 and v.1.19 (original and hotfix versions) will be accepted

- v1.19 of the variation eAF is duplicating fields in Section 2 Products Concerned By This Application, if a second Invented Name for an MRP submission is added the form adds a second section, but also adds fields for MA Holder Name and MA Number in two places, not replicating the structure of the original section (see screenshots below and attached eAF). This is issue is persisting also when 'National authorisation' is selected. For national variations the MRP field should be ignored.

- v1.19 of the variation eAF is not displaying the name of the certain z scopes correctly in the summary box and in the 'present and proposed' section. This is a very complex defect and hence there is no immediate fix provided for the variation form as part of the hotfix. Please provide the details in the precise scope field and describe the issue on the cover letter.

Variation	Selected
z)	2
B.I.e.3	1
B.I.e.2	1

			Procedu
☒	**B.I.e.2**	**Introduction of a post approval change management protocol related to the active substance**	II
☒	z)	Other variation	☒ IA ☐

- The location within the dossier does not change due to the different format

- You may use the same file names as in the past

- Due to a possibly higher number of attached annexes it is highly recommend to follow this naming convention:

  - eCTD and NeeS: **cc-form.pdf** will contain the eAF PDF file, XML data will extracted from there. If any additional file is named differently it will become very easy for NCAs to identify the file to be extracted
    All annexed files should make use of the variable part to identify different content, e.g. annex on section 2.6.2 or proof of payment or annex 5.19:
    cc-form-annex2-6-2.pdf, cc-form-proofpayment.pdf , cc-form-annex-5-19.pdf

  - **In MRP/DCP one common application form is highly recommended.**

  - VNeeS: As there no detailed naming convention exists it is recommended to adapt the file names as it is required for human medicinal products

eAF – export and import of data

- Data can be extracted from the PDF file in XML format at any time

- If the form has been 'locked', neither the applicant nor the receiving agency is able to make changes to the form. However, the marked buttons at the far end of the form are still working

```xml
◢ <xfa:data xmlns:xfa="http://www.xfa.org/schema/xfa-data/1.0/">
    ◢ <maa:eu_application_form xsi:schemaLocation="http://www.ema.eaf/maa/maa_human.xsd"
        xmlns:xsi="http://www.w3.org/2001/XMLSchemainstance" xmlns:rdm="http://www.ema.eaf/dictionary
        xmlns:maa="http://www.ema.eaf/maa/">
      ▷ <maa:envelope>…</maa:envelope>
      ◢ <maa:initial-application-form-human>
        ▷ <maa:scientific-advice>…</maa:scientific-advice>
        ▷ <maa:declaration>…</maa:declaration>
        ◢ <maa:chapter-1>
          ◢ <maa:procedure-type>
            ▷ <maa:centralised-procedure>…</maa:centralised-procedure>
            ◢ <maa:mutual-recognition-procedure>
                <rdm:selected>1</rdm:selected>
                <rdm:selected_scope></rdm:selected_scope>
                <rdm:procedure-number>DE/H/1234/001/MR</rdm:procedure-number>
                <rdm:reference-member-state>100000000403|Germany</rdm:reference-member-state>
                <rdm:date-of-authorisation>2014-02-26</rdm:date-of-authorisation>
                <rdm:market-authorisation-number>12345.00.00</rdm:market-authorisation-number>
                <rdm:first-use>1</rdm:first-use>
                <rdm:waiver-amendment-psur></rdm:waiver-amendment-psur>
              ▷ <rdm:member-renewals>…</rdm:member-renewals>
            </maa:mutual-recognition-procedure>
            ▷ <maa:decentralised-procedure>…</maa:decentralised-procedure>
            ▷ <maa:national-procedure>…</maa:national-procedure>
          </maa:procedure-type>
```

| Validate Form | Jump to selected | Error Color Scheme ⦿Yellow ○Red | Save Form | Print Form | Export XML | Import XML | Update lists |

eAF – export and import of data

- Exported data can be imported into an empty form.

- Using this functionality you can "copy" a filled unlocked form e.g. after a version update. Be aware that intellectual control is essential and most likely manual re-work becomes necessary.

- You are able to import the data also in case of a locked form. But the import includes the signature image as well and the form remains locked.
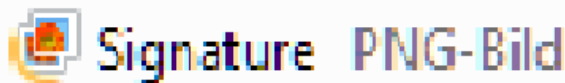
Signature PNG-Bild

This form was authorised following company policies by Dr. K. Menges, Senior Reg. Affairs Manager of BfArM with authorisation to sign. The signature is in file.

```
▷ <maa:signature>…</maa:signature>
◁ <maa:dec-signature href="" xfa:contentType="image/png">
    iVBORw0KGgoAAAANSUhEUgAABdwAAAEsCAIAAABWiuY5AAAACXBIWXMAAA7EAAAOxAGVKw4bAAAA
    B3RJTUUH3wkeDQcreU+6UwAAAAd0RVh0QXV0aG9yAKmuzEgAAAAMdEVYdERlc2NyaXB0aW9uABMJ
    ISMAAAAKdEVYdENvcHlyaWdodACsD8w6AAAADnRFWHRDcmVhdGlvbiB0aW11ADX3DwkAAAAJdEVY
    dFNvZnR3YXJlAF1w/zoAAAALdEVYdERpc2NsYW1tZXIAt8C0jwAAAh0RVh0V2Fybm1uZwDAG+aH
    AAAAB3RFWHRTb3VyY2UA9f+D6wAAAAh0RVh0Q29tbWVudADDzJa/AAAABnRFWHRUaXRsZZQCo7tIn
    AAAgAElEQVR4nOzd6XMc15nn+29m1obCvpIuG8iaYmyJC++yu+2e9rinozti3kzE//Qfun3Tf3P/i
    ztyYuOOJnuix3d35E2bLUkkhxE3cAJBZiR62ZeV8852R1FUFakiUVSfw+L0jkQaGqGq7/i
    kKYpIiIiIiIiIiLy7Qr7/QREREREERERA4iTcqIiIiIiIiiPSBJmVEREEREREREpPpAkzIiIiIi
    IiIiIn2gSRkREREREREkT7QpIyIiIiIiIiISB9oUkZEREEREERpA80KSMiIiIiIiIi0gealBER
    ERERER6QNNyoiIiIIiIiI9IEmZURERE
    jIiIiIiIiThIH2hSRkREREREREkDzQpIyIi                         EREIiIiIiIj0
    gSZ1REREREREET6QJMyIiIiIiIiIiJ9oEkZ                         aFJGREREERE
    RKQPNCkjIiIiIiIiItIHmpQREREREREEekDTcqIiIiIiIiIiPSBJmVERERERERERPpAkzIiIiIi
    IiIiIn2gSRkREREREREkT7QpIyIiIiIiIiISB9oUkZEREEREREpA80KSMiIiIiIiIi0gealBER
    ERERER6QNNyoiIiIIiIiI9IEmZURERERERE+kCTMiIiIiIiIiIiIifaBJGREREREERGRPtCk
    jIiIiIiIiThIH2hSRkREREREESkDzQpIyIiIiIiIiLSB5qUERERERERERHpA03KiIiIiIiIiIj0
    gSZ1REREREREET6QJMyIiIiIiIiIiJ9oEkZEREREREREZE+0KSMiIiIiIiIIiEgfaFJGREREERE
    RKQPNCkjIiIiIiIiItIHmpQREREREREEekDTcqIiIiIiIiIiPSBJmVERERERERERPpAkzIiIiIi
    IiIiIp106BcT6JuU7dxPz=t06p5p1Rky7hmbuOsoaHUftrMvO4a+9EFQUF0nS7D7umc8M292He0/f
    ```

XML extract

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- Will applicants be informed of upcoming updates to the AF some time in advance of it coming into force?
  Yes, please check eAF - website

- If so, how long in advance?
  The release schedule is available in the eAF webpage. For example; the date for version 1.20 has been published (15.04.2015)

- What if we have prepared a variation with the electronic AF and while finalising all the documentation for the submission there is an update to the AF (a new version). For how long will the previous version be accepted for submission?
  A transitional period is available – please find details for version 1.20 in this presentation.

- Will there be a technical possibility to update the AF to the new version without losing the variation/product/company specific data added?
  It is possible to export and import the user inserted data to the new version of the form, however, updates of the underlying data exchange standard (XML-data) can mean that some fields are not correctly imported.
  Normally usability changes will have no impact on the data imports, however, e.g. v. 01.20 will change the DES

Questions – Form versions

- Is it possible to use current AF (paper version) within the eCTD for the MAAs submitted till 31.12.2015 till the end of the procedure? Namely, if there is a change impacting AF during the procedure, it would be a double work (first filling out paper version and then complete eAF from the scratch). Also, some MSs could have comment on eAF whereas not having them till that moment on paper version of the AF?
  There is no need to change the format or the version of the application in the middle of the procedure.

- Is it expected with eAF becoming mandatory 1/1/16, that already approved paper AF needs to be converted to eAF, when submitting a baseline sequence next year to start eCTD lifecycle?
  If the baseline is provided with a **new** regulatory activity it should contain the latest version of the eAF. It will become mandatory to use the eAFs for all human and veterinary initial, variation and renewal applications from 1 January 2016.

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- Will the guidance and Q&A documents be updated before end of the year, when?
Regular updates are planned and next update is expected in January 2016

- Will the process to lock the form be changed (currently import of a signature image needed), e.g. by a button or tick box?
There are no existing CRs to change this functionality

- What does this mean regarding the legal relevance of the signature image and what is required to authorise the form by the MAH from a legal perspective? "This image will not work as a digital advanced or qualified electronic signature nor can replace requirements of wet signed forms."
Please check national requirements for signatures.

- Does the scanned image work as a digital advanced or qualified electronic signature? Can it replace requirements of wet signed forms?
Please check national requirements for signatures

- We know that a qualified certificate is needed to sign EMA forms. Therefore we take into account as an option to use SAFE BioPharma certificates. But I'm unsure if they fulfill the EMA requirements. I saw that there is a list of TrustCenters, but I don't find no non-country-specific providers. Where can I check if we are able to use SAFE for EMA submissions?
The forms should be signed using a scanned image of a signature. There is no need to use qualified signatures for eAFs submitted to the EMA for Centralised Procedure applications.

- Should we use one single (common) form for all Member States in the MRP/DCP applications?
  Yes, this is highly recommended. There are no country specific electronic application forms available.

- Is one single (common) form in English language accepted?
  Yes, there are no national translations available; in MRP/DCP all member states should accept the application form in common language. Please consult CMDh and CMDv web-sites.

- Are additional paper forms (with wet-ink signature) required in any Member State?
  Please check national requirements; harmonisation of the signature requirements is not in the remit of the eAF MG. Questions on national requirements can be forwarded to eaf@ema.europa.eu or directly to the relevant NCA

- Can we submit a common and unique e-AF for MRP/DCP? How will it be managed?
  Yes, this is highly recommended. The file name will be **common-form.pdf** (not using the variable part)

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- We use a specific AF for Homeopathic medicinal products' Marketing Authorisation Applications. Will a specific eAF be published and when?
This specific form is currently not adapted for eAF purpose. It need to be clarified whether existing differences and additional needs can be accommodated in the eAF MAA (hum and vet).

- Use of eCTD is not mandatory in the NCA to which I'm submitting to. Do I still have to use the eAF?
Yes, the use of eAF will become mandatory for all submission formats including paper based applications.

- Will each National Competent Authority decide whether the eAF should be compulsory or not for National?
The NTA application forms will be replaced by the eAFs for all procedure types. If you have any questions, please contact the relevant NCA.

- In DCP/MRP an AF signed by multiple responsible persons is needed for communication with specific Authorities (could be initial submission or renewal or variation). How this can be done with 1 AF? Or it is possible only with multiple AFs where only signatory person is different?
  Ideally provide a single contact point. For those NCAs that require multiple contact persons include a separate annex with the contact details.

- Using a single eAF for MRPs/DCPs for all member states: In particular, information on Section 1, Name and address of the Applicant/MA holder – within an MRP/DCP submission, the Application/MA holder may differ per member state. This section is currently not replicable, therefore we are unable to add differing Applicants/MA holders within one single form. We suggest making the applicant section of the eAF repeatable.
  This is an existing change request to the form and we are hoping to improve this section in the next release of the forms (v. 01.20)

- Will the national requirements for local language form requirements remain, and if so, what is the suggested workaround for this.
Please contact the relevant NCA. There are different approaches available. eAF forms are only available in English according to the eSubmission Roadmap

- Can you confirm that there is no requirement for national translations of the eAF in any procedure type.
Yes, it is highly recommended to provide a common form in common language. NCAs are required to accept the common version of the form. At the moment, we cannot exclude that some NCA require an additional document / translation in the workingdocuments folder or via a portal

- eAF will become mandatory for all type of licenses (Human) on 01-Jan-2016. Is there any visibility on whether national authorities will continue to require filling in a specific form linked to their own database (for example in Spain, currently the Application Forms are generated by the authorities database, with additional requirements and validation steps than those present in the eAF)
Please contact the relevant NCA; send feedback to eaf@ema.europa.eu

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- Currently they are countries which are requesting originally signed AFs (without national translation required), to be submitted (irrespective if the submission is done via CESP or not). Will this be still necessary? If yes, the unsigned eAF will be printed, signed and submitted?
  The eAF does not change the wet signature requirements at the NCAs. Please check the national requirements for wet signatures to avoid validation issues.

- What format of AF should I submit in Countries where originally signed AF in paper format is required according to national requirements?
  Please contact the relevant NCA whether there is a need for a wet signed form in parallel. Scanned eAF are invalid and will be rejected.

- National wet signed Application Form requirements. We understand that the requirement for wet signed copies of the Application Form will remain. Following communication with the EMA, we have proposed the provision of printed versions of the eAF countersigned in ink, however, some countries have requested that a PDF scan of the wet signed version be included within the eCTD/NeeS. We question the requirement and value in providing this as the eAF and wet signed requirements will have been met.
  These issue will be communicated to CMDh and CMDv because it cannot be solved within eAF MG.

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- To what extent does country-specific information have to be included in the eAF?
  For some information (e.g. for MAH, MA number) provision is made for, but national particulars cannot be entered for other data (e.g. invented name, proof of payment, contact info). This seems to be an inconsistent approach which makes it difficult for companies to decide on a clear internal strategy. It can also lead to slightly different application forms in the concerned member states. Thus it would be helpful to have some room to move (e.g. extend the "see annex A/B" workaround also to other sections and not just use it for MAH, MA number). It would also be interesting to hear how other companies deal with country-specific information, and what authorities actually expect.
  It is recommended to prepare additional annexes, if the form does not provide sufficient possibilities itself. Annexes based on section 5 can be indicated in the respective section and need to be added in Module 1.2 anyway. A naming convention is recommended and will be added to the validation criteria. Due to the high variability of needs, this will not be added to become P/F.

- I am still submitting in paper should I prepare the eAF to send to the agency electronically in parallel and then print it to go with the paper?
  eAF will completely replace the NTA application forms. Please check national submission requirements if parallel electronic submission is required.

- I have seen some colleagues who are already preparing the eAF but after completion they will print the form to sign and scan it to be included in the submission. What suggestion is there to get around the electronic version of their signature, which is required to validate the form?
  Printing and scanning the signed form should only be done for paper submissions as this way the eAF will become a flat PDF.

- Would the EMA agree that a master form can be prepared containing general entries that will not change, which can be 'Saved As' each time. This would remove the need for the author to update each of the drop downs etc. each time they need to complete the form? Only the details relating to the current submission would be required i.e. application number, description etc?

  It is recommended that a template is created by the MAHs/applicants that can be used over and again without a need to refill all the information. It is however very important to observe if new versions of the forms become available. In those cases the templates will need to be updated.

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- In the variations eAF it is possible to select the types of change(s)/variation categories. Nevertheless the relevant page(s) from the Guideline for this/these change(s) still need to be attached and the relevant boxes for conditions and documentation (both for Type IA and Type IB) need to be ticked. Are there any plans to integrate this into the eAF? Any timelines available?
  There is an existing change request to improve the variations form. The proposed change is however a major change to the variation form and it is likely that this will not be implemented before the introduction of the Single Submission Portal

- For variation AF how the Classification Guideline table will be added?
  The classification Guideline table should be added as a separate document annexed to the application form. It should be provided in the same folder as the application form, clearly named as Classification Guideline

- eAF doesn't contain the condition(s) to which variation has to comply and documentation(s) which has to be submitted acc to type of variation. How can be this part added to the variation form?
  The conditions should be provided as a separate document annexed to the application form. It should be provided in the same folder as the application form, clearly named as Classification Guideline

- How to represent deleted text in eAF, as strikethrough option is not available
In the section of present/proposed text in the variation form it is possible to paste in text with strike trough formatted characters using RTF.

PRESENT[9,10]	PROPOSED[9,10]	i
Hinweise • Bislang sind keine weiteren Dokumente, die in der Sitzung verwendet werden könnten (z B. ~~aktuelles Bild der Systemlandschaft)~~ ~~eingegangen~~	**Hinweise** • Bislang sind keine weiteren Dokumente, die in der Sitzung verwendet werden könnten (z B. ~~aktuelles Bild der Systemlandschaft)~~ ~~eingegangen~~	+ -

- Section 1: Why does "variation procedure number" becomes visible when choosing national procedure? This is not applicable for national procedures
Also in case of purely national variations these cases may have a procedure number. The information note may be added to not confuse people.

- Section 2: For national procedures the set-up for MA holder name and MA number is not including Member state. The only section for national procedures where member state is present is in the section 1 "Name and address of contact person". Why is it not aligned with the same set-up as for National Authorisation in MRP/DCP?
This deficiency will be managed with in the next version. currently a workaround (additional annex) is required.

- Section 3: "Scope and background" and "Present and proposed": Will it become possible to insert a table? It would create a better overview and ease the readability
Currently you can use text lines and insert blanks to structure the layout similarly; a CR will be discussed

- Will it become possible to integrate the dossier requirements into the eAF for variations?
To be responded in writing. More details on the request required.

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Variation application form / Formatting within present-proposed table:

- How can we fill the present propose-table in a more effective way?

- Concerns: The fact that no table-formatted content can be added in the text fields, forces the users to add screenshots instead; which is a tedious and time-consuming task (no copy-paste can be done, each screenshot needs to be saved as a file before being included in the image field). In addition this approach is not user friendly, since no further edits are possible and also the image could be of bad quality and low readability. In addition, the image fields are not adapting to the size of the images included, which means that the screenshots have to match with the size of the field (200 pixels of height) to be readable. This adds to the complexity as many screenshots have to be created to cover big tables.
  More complex descriptions can be provided in an annex.

- How can we add table-formatted data in the present-proposed table? see previous question
  How can we copy-paste an Image? yes, you can select an image from the file system per each cell
  How can we add multiple pictures in the same image field? no, just one image per cell. The cells are repeatable
  How can we adapt the picture to the size of the field ? no, the image cannot be enlarged
  How can we alternate text fields and image fields in the present-proposed-table (e.g. text-image-text-image-text)? no, not with one section of present/proposed. You need to repeat the section entirely.
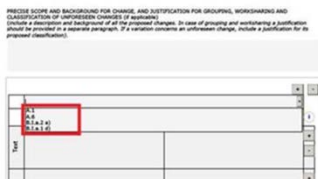
- Variation drop-down for present-proposed table:
  How can we select multiple variations for one section of the present-proposed table (e.g. several changes might be located in the same section of a document)? no, there is only one reference option provided.

- How can we reflect "Editorial Changes" in the present-proposed table and which drop-down option we choose for this type of changes?
  Editorial changes should be described in the present-proposed table, but are not necessarily directly related to a variation editorial changes.

Variation application form / Formatting within present-proposed table:

- **Copy of the relevant pages from the Guideline :/** How can we provide the copy of the relevant pages from the Guideline?

3. TYPES OF CHANGE(S)

☒ Copy of the relevant page(s) from the Guideline for this/these change(s) is att conditions and documentation (both for Type IA and Type IB) are ticked.

- In situations that require an extensive explanation in a specific comment field, how can we proceed if we do not have enough space for our clarifications (e.g. some comment fields only accepts 50 characters)?
  More complex descriptions and copies of the relevant conditions need be provided in an annex.

- Can you make this a future improvement that the copy of the relevant page guideline will automatically be attached as annex to the AF?
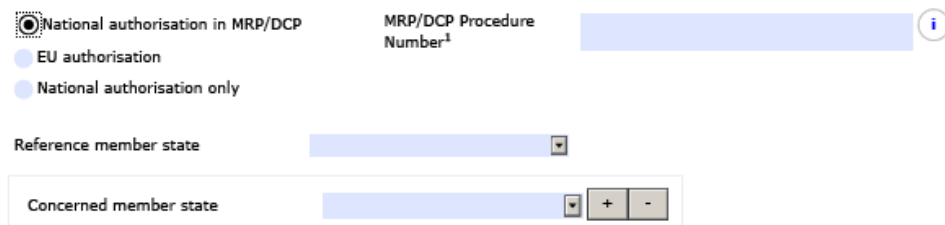 Not with the current eAF versions; a CR will be discussed

- Section 1: section for MA numbers: only the CMS countries are listed – shouldn't the RMS be listed as well? How do we fill in the MA number for the RMS?
  If you select MRP the additional lines for RMS and procedure number will be displayed. This was a known defect that has now been fixed in the release 01.19.0.1 released on 30th November 2015.

- Section 2: Active substance manufacturers: it is not possible to add a function of the manufacturer – how do you discriminate between e.g. manufacturers of intermediates for API and the actual API manufacturer?
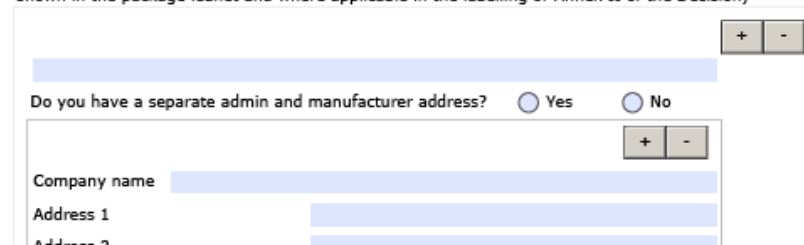 You can describe the role of the manufacturer in the first line. The section can be repeated as often as needed.

Questions – Renewal form

- Composition: How do you fill in details for an excipient that has been approved with the amount "q.s."?
  Q.S was introduced as quantity operator in the eAFs and will now allow to describe the limits precisely. The guidance will be updated to reflect this change.

- Renewal form – revision June 2015; Is there some kind of overview which explains all abbreviations used in the drop down list. For example, at section 1, when you need to complete the composition of the active substances for a tablet, you cannot choose xx mg/tablet. There is the possibility of mg/U, but I'm not sure what the "U" stands for, is it unit?
  Values are re-used from EUTCT. Details can be retrieved from term details. In general, the abbreviations should follow common standards, i.e. The International System of Units

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- In section, 2.6.1 Qualitative and Quantitative composition in terms of the active substance(s) and the excipient(s) there is no space to include a note to the Qualitative and Quantitative composition after the excipients list.

  At the moment you have an option to add a note above of each list.

		+	-
In section, 2.6.1 Qualitative and Quantitative composition in terms of the active substance(s) and the excipient(s) there is no space to include a note to the Quali			

Name of Excipient	Quantity / Unit	Reference / Monograph Standard	+

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- If possible, I would need the confirmation that the eAF will be compulsory to use in MRP/DCP procedures from 1 January 2016 also for Vet procedure. In that case, how it will be handled by National Competent Authorities which are still requiring hard copies?
  Yes, the use of the eAFs is also mandatory for Veterinary submissions as per the eSubmission Roadmap; Please contact the relevant NCA for national requirements.

- Pharmaceutical form: If our pharmaceutical form is not listed in the form, what should we do?
  Please follow the defined missing term request process. Details are available on the eAF website.

- Active substance: When we click to the drop down window, there are no active substances to choose. Not even with writing the active substance and clicking the bottom "search". The same happens with excipients
  Occasionally there are issues with the connection to the EUTCT web services. If this happens, please save the form and reopen to check if the connection has returned. If the issue persists consult your IT support to check if your internet connection is working.

- Documents appended to this application: There are some boxes we don't need to mark as they are not applicable for us. However, if we don't mark all of them a validation error appears. What should we do?
  Occasionally the built in business validation rules have been interpreted incorrectly when the forms were built. You should report any unusual form validation errors to eAF@ema.europa.eu. Please note that the form validation errors are there to guide you to fill in the application correctly and sometimes it is perfectly acceptable to leave some validation errors especially when information is provided on a separate annex to the application form.

- In terms of composition, how do I address situations when label claimed active substance is a base while the actual API used is a salt as per below example:

Material	Function	Quantity	Unit	Specification
Fluoxetine hydrochloride Equivalent to Fluoxetine	Active substance	22.4 20.0	mg	E.P

Currently the AF is completed as per below:

2.6.1 Qualitative and Quantitative composition in terms of the active substance(s) and the excipient(s):

A note should be given as to which quantity the composition refers: 1 tablet
List the active substance(s) separately from the excipient(s):

Name of active substance(s)*	Quantity	Unit	Reference/Monograph standard
Fluoxetine as	20.0	mg	
Fluoxetine hydrochloride	22.4	mg	Eur.Ph

Detailed instructions how to add salt/hydrate format in section 2.1.2 of the Initial MAA for are available in the eAF Q&A document and in the technical guidance document.

- **Fast web view** / Our eCTD generating software automatically saves all pdfs within the eCTD with fast web view enabled, however in the case of signed eAFs this renders them unviewable, there is no way to switch this off. The workaround we have employed is to "print" the signed eAF to pdf which is then used in the eCTD. The "printed" pdf can have the fast web view enabled and remain readable even when output as part of an eCTD. My question is two fold

  Will this still be acceptable when the form becomes mandatory? When printing to PDF the bookmarks are lost, but we have been reintroducing them manually; if print to pdf is an option for eAF forms, is it necessary to reintroduce the bookmarks?

  Printing and scanning to overcome the fast web view BP warning will destroy the XML-backbone (XML data) and results in an incompliant eAF which will be rejected. The eCTD validation best practise warnings can be ignored but the forms must be provided as real eAFs with xml. Flat PDFs will not be accepted.

- **eAF for initial MA application /** Section 1.3 for the legal basis cannot be completed (the boxes which should normally be ticked (e.g. 1.3.1 for Art. 12(3)) do not pop up);
  Please provide more details of this issue ideally with screenshots comparing it to the NTA application form.

- For the GMP-related information (5.9 and 5.10), there is a technical mismatch between the information ticked in the eAF and the automatic ticked boxes in the Annex to the eAF.
  We are unable to reproduce this issue. Could you please provide us a copy of the form where this issue is present for further investigation.

- The section "Active Substance" is difficult to fill in especially for immunological products.
  The AS descriptions available in the database most often do not match very well with the description in the product information. Clear instructions on the level of detail that is required should be given. Is a workaround available to indicate the immunological active substances in more detail?
  The same workaround principle applies as for other sections. Please highlight a respective notification in your cover letter.

- Why is there no possibility any more to add a contact person for the Scientific Service for the CP? The User guide states the following: "In centralised procedure a single contact person should be indicated for the scientific service".
  For ease of contacting the applicant only single contact person for each procedure should be provided. Contact details can contain an email address to a shared mailbox if multiple persons are dealing with the application on the applicant side.

- In section 2 / Product name/strength/form is not listed in the form as there is a reference to Annex A.
  MA Holder name: reference to Annex A is given as option, however Annex A does not list MAH in Annex A for a CP.
  As for CP there is only ever one MAH, this field can be filled in the eAF and the rest of the information is provided in the Annex.

- Regarding section 2.5.2 and 2.5.3: does the term "quality control" also includes release testing, and if so, when it comes to the release testing of the medicinal product, are then sites listed twice, once in 2.5.1.2 and 2.5.2? Yes, release testing of the finished product is part of Quality testing. This activity is only linked to sites performing Batch Control testing arrangements in relation to the Batch Release of the product as per requirements of Article 51 of Directive 2001/83/EC. As such a site may perform both release testing under 2.5.1.2 and "normal" QC-FP activities under 2.5.2 which are not linked to the batch release. In this case the site(s) will be listed twice i.e. under each section. However, if the site only performs one or the other quality control testing only, the site(s) will then need to be listed in the relevant section depending on the QC-FP activity l testing arrangements in relation to the Batch Release of the product as. Sometimes, sites perform both kinds of testing activities however only sites located in the EEA or where an MRA or ACAA arrangement is in place can be listed in 2.5.1.2. Third country sites (USA and any other country outside the EEA/MRA/ACAA) cannot perform this activity and should therefore not be listed under 2.5.1.2. These sites are only authorised to perform QC-FP activities not related to the Batch Release.

- Could you probably address how notifications, e.g. art 61(3) will be handled in the future?
  The eAF does not introduce change to how art. 61(3) notifications are handled

MAA Application form:

- Section 2.2.1: The "OK/Clear/Cancel" button doesn't work?
  Section 2.2.1 is auto-populated from the declaration section.

- Section 2.5.3: The field "Name of the manufacturer if different form the above" is mandatory – but "Name of the CEP holder" isn't – why is that, and how can a field containing "if" be mandatory?
  More information and details required to allow investigation

- For product with more than one API: How do you list the strength of the product in the applications forms? As it is now you will have to list the amount of the individual APIs in separate rows with no link to the API?
  Example of how the form could be filled below

Product (invented) name   Wonderdrug 100mg/10mg

Pharmaceutical Form: Capsule, hard

Strength: Units
100   mg

Active Substance(s):
PARACETAMOL

Add Active Substance(s)

Pharmaceutical Form:

Strength: Units
10mg   mg

Active Substance(s):
CODEINE

- In the case of a very urgent submission (the same day that the problem is encountered) and the eAF cannot be opened, nothing is not working properly, I cannot sign the document, etc... How long is the response time for the eAF team to come back to me and solve the problem?
  Please contact eAF@ema.europa.eu immediately highlighting the urgency of the query in the message.

- Would there be the possibility for very exceptional cases to submit the latest AF version 2015 and put a comment in CESP? What would be your proposed solution for such a situation?
  Please be aware that the RMS may ask for a compliant version during validation. The EMA will reject all non eAFs.

- **Publishing requirement of eAF /** Is there a requirement for the eAF to be supplied in a published submission only (i.e. eCTD /NeeS)? Or can the eAF be submitted via CD as a standalone document too? Please submit the eAF only within a eCTD / NeeS / VNeeS submission. However, if your dossier format is still paper based, a separate electronic submission may be appropriate if agreed with the responsible NCA.

Contact

Please send any questions to

eaf@ema.europa.eu or the responsible NCA contact