



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 October 2010
EMA/665231/2008 Rev. 1

Implementation plan for the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final Rev. 2)

Implementation plan revision 1

1. Background

The 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final Rev. 2) describes the new aspects of Safety Message processing, ICSR validation and acknowledgment generation in the European Economic Area (EEA). It has been prepared by the EudraVigilance Expert Working Group (EV-EWG) in response to the EudraVigilance Action Plan (EMEA/82645/2007), which was adopted by the Heads of Medicines Agencies (HMA-Human) in Bonn, Germany in April 2007 and endorsed by the European Medicines Agency (EMA) Management Board in London, UK, in June 2007.

The revised Note supersedes the business rules and validation steps as described in the 'Note for guidance – *EudraVigilance Human Version 7.0* – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final). It represents a consensus view and is applicable to all stakeholders exchanging Safety/Acknowledgement Messages and ICSRs electronically in the EEA in line with EU legislation¹.

2. Scope of the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final Rev. 2)

The scope of the revised note for guidance is to improve the quality and consistency of ICSRs reported electronically. This has been achieved by strengthening of the validation processes of ICH E2B(R2) data elements and by making mandatory the population of certain ICH E2B(R2) data elements in the ICSRs.

The improvement of the data quality is of major importance as regards the following aspects:

¹ Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 of The Rules Governing Medicinal Products in the European Union.



- Supporting the EU pharmacovigilance and risk management activities mainly in the area of signal detection, case assessment and the evaluation of potential safety issues;
- Preparing for the implementation of the EudraVigilance Access Policy;
- Monitoring the safety of patients enrolled in clinical trials and more specifically allowing for the adequate association of reported suspected unexpected adverse reactions (SUSARs) with the relevant interventional clinical trial(s), the investigational medicinal product(s) (IMPs) and specific countries.

A summary of the revised validation rules and of the new mandatory ICH E2B(R2) data elements in ICSRs is provided in Annex 1.

3. Objective of the implementation plan

The objective of this implementation plan is to facilitate a coordinated implementation approach between all stakeholders regarding the process of putting the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) (EMA/H/20665/04/Final Rev 2)' into operation. Since a large number of stakeholders in the EEA apply the electronic transmission of ICSRs, any changes of the validation procedures require a common approach to avoid disruptions in the data exchange process. Therefore, all stakeholders will need to follow the implementation approach as outlined in Chapter 4.

4. Implementation approach

The implementation of the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final Rev. 1 and Rev. 2) should be approached by all stakeholders in a stepwise manner based on the following two principles:

4.1. Step 1: Adaptation of Data Entry and Data Management Procedures

The revised business rules represent a best practice guide related to the preparation and electronic exchange of ICSRs.

In preparing and processing ICSRs, all stakeholders should apply the revised business rules published in November 2009 (EMA/H/20665/04/Final **Rev. 1**) **as of 1 June 2010** in accordance with the respective implementation plan.

This approach does not require any immediate technical changes to the pharmacovigilance systems in use by stakeholders but refers in the first instance to the data entry and management practices of each stakeholder, which require alignment with the revised business rules.

From **1 June 2010**, the Agency will perform routine data-quality control, based on the updated business rules and validation processes, as described in the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final **Rev. 1**) published in November 2009.

Senders (Marketing Authorisation Holders (MAHs)/Sponsors of interventional clinical trials and non-interventional studies and National Competent Authorities (NCAs)) will receive a monthly notification with line listings of ICSRs, which do not comply with the new mandatory data elements and validation rules as described in the 'Note for guidance **Rev. 1**' (further details are provided in Appendix A of that version). More specifically, for:

- ICSRs classified as 'Error Reports', originating in the EEA and reported initially by MAHs/Sponsors to NCAs, the Agency will send line listings directly to the NCAs concerned. NCAs will liaise with the MAHs/Sponsors to ensure that a corrected version of the 'Error Reports' is retransmitted to them. The NCA will subsequently forward the corrected reports to the appropriate EudraVigilance module taking into account the current reporting rules as set out in EU legislation and Volume 9A/Volume 10 of The Rules Governing Medicinal Products in the European Union. 'Error Reports' should be corrected and transmitted immediately and no later than 15 days following the receipt of the Agency's monthly notifications.
- ICSRs classified as 'Error Reports' and originating outside the EEA, the MAHs/Sponsors should correct the reports and retransmit them electronically to the appropriate EudraVigilance module immediately and no later than 15 days following the receipt of the Agency's monthly notifications.

The currently established technical validation processes as described in the 'Note for guidance – EudraVigilance Human Version 7.0 – Processing of safety messages and individual case safety reports (ICSRs) (EMA/H/20665/04/Final)' remain unchanged.

ICSRs which do not comply with the new validation processes and mandatory data elements detailed in the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final **Rev. 1**) will currently not be highlighted as 'Error Reports' or 'Reports with Warnings' in the respective Acknowledgement Messages.

4.2. Step 2: Technical adaptations of current pharmacovigilance systems

Technical changes based on the revised business rules require a coordinated approach in the EEA to avoid major disruptions in the electronic exchange of ICSRs. **The technical implementation of the revised business rules (EMA/H/20665/04/Final Rev. 2, which includes the revision 1 updates) will take place on 7 February 2011 at 09:00 AM GMT.**

From **7 February 2011**, the validation processes and mandatory business rules, as described in the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final **Rev. 2**) published in October 2010 **will be technically implemented in EudraVigilance.**

This means that ICSRs which do not comply with the new validation processes and mandatory data elements detailed in the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final **Rev. 2**) will be classified as 'Error Reports' or 'Reports with Warnings' in the respective Acknowledgement Messages.

A corrected version of the affected ICSRs, classified as 'Error Reports' according to the revised guidance, should be retransmitted electronically by the Sender to the appropriate EudraVigilance module immediately. The expedited reporting timelines remain unaffected even if an error is detected through the validation processes.

In addition, the safety message reference to the Document Type Definition (DTD) specification version 2.1 needs to be updated from 'eudravigilance.emea.europa.eu' to 'eudravigilance.ema.europa.eu' due to the new domain name (ema) for the European Medicines Agency. **The new safety message reference should be used from 09:00 AM GMT on 7 February 2011.** Note that after this time messages referencing the EMEA domain will be rejected with an '03' acknowledgement message. Technical instructions regarding the implementation of the new domain name are provided in Annex 2.

To facilitate the technical implementation of the revised business rules and the new domain name, **the updated EudraVigilance Pre-production (Test) environment will be released to stakeholders**

from 09:00 AM GMT on 3 November 2010. The revised business rules will be based on the latest version of the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final **Rev. 2**) published in October 2010.

As highlighted in Annex 3, in order to be able to test against the revised business rules, stakeholders will need to use the new domain name in the EudraVigilance Pre-production (Test) environment.

Test messages sent using the previous domain name (eudravigilance.emea.europa.eu) will be processed and validated against the current business rules, which were put into operation in October 2004 (EMA/H/20665/04/Final), and which will be valid until 7 February 2011 09:00 AM GMT.

5. Training

Training as regards the requirements outlined in the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' (EMA/H/20665/04/Final **Rev. 2**) will be provided in the frame of the EudraVigilance training programme and the EudraVigilance Information Days.

Annex 1 Summary of new mandatory ICH E2B(R2) data elements and validation rules

Updates to Revision 1 of the 'Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)' are presented in blue in this document.

NEW MANDATORY ICH E2B(R2) DATA ELEMENTS		
Validation outcome	Description	Objectives
Classified as "error" in case of non compliance	<ul style="list-style-type: none"> Identification of the country of the primary source (ICH E2B(R2) A.1.1) 	<ul style="list-style-type: none"> Systematic identification of the primary source country in the ICSRs
	<ul style="list-style-type: none"> Primary source qualification (ICH E2B(R2) A.2.1.4) 	<ul style="list-style-type: none"> Identification of healthcare professional reports and non-healthcare professional reports
	<ul style="list-style-type: none"> Serious (ICH E2B(R2) A.1.5.1) 	<ul style="list-style-type: none"> Differentiation of serious reports from non-serious reports
	<ul style="list-style-type: none"> Seriousness criteria (for serious reports) (ICH E2B(R2) A.1.5.2) 	<ul style="list-style-type: none"> Identification of the seriousness criteria in ICSRs
	<ul style="list-style-type: none"> Outcome of reaction/event at the time of the last observation (ICH E2B(R2) B.2.i.8) 	<ul style="list-style-type: none"> Identification of fatal reactions Provide information on outcome for each reaction Data quality control
	<ul style="list-style-type: none"> Characterisation of drug role (ICH E2B(R2)B.4.k.1) 	<ul style="list-style-type: none"> Systematic identification of the drug role (Suspect, Concomitant, Interacting)
	<ul style="list-style-type: none"> Active substance name (for reports submitted to the EudraVigilance Clinical Trial Module when the drug is considered suspect or interacting) (ICH E2B(R2) B.4.k.2.2) 	<ul style="list-style-type: none"> Identification of the suspected or interacting active substances in reports originating from interventional clinical trials
	<ul style="list-style-type: none"> Relatedness of Drug to Reaction(s)/Event(s) (ICH E2B(R2) B.4.k.18) for the suspect/interacting medicinal 	<ul style="list-style-type: none"> Distinction of adverse reactions related to the suspected/interacting medicinal product(s) from other

NEW MANDATORY ICH E2B(R2) DATA ELEMENTS

Validation outcome	Description	Objectives
	product(s) for reports submitted to the EudraVigilance Clinical Trial Module (EVCTM)	events/reactions unrelated to the suspected/interacting medicinal product(s)
Classified as “warning” in case of non compliance	<ul style="list-style-type: none"> Active substance name (for reports submitted to the EudraVigilance Post-Authorisation Module when the drug is considered suspect or interacting) (ICH E2B(R2) B.4.k.2.2) 	<ul style="list-style-type: none"> Identification of the suspected or interacting active substances in spontaneous reports or reports from non-interventional studies

NEW VALIDATION RULES

Validation outcome	Description	Objectives
Classified as “error” in case of non compliance	<ul style="list-style-type: none"> All reported country names, including the first part of the ‘Worldwide unique case identification number’, should be valid ISO3166 country codes 	<ul style="list-style-type: none"> Standardisation of reported data Consistency check with primary source country
	<ul style="list-style-type: none"> For ICSRs submitted to EVPM and EVCTM spontaneous reports and reports originating from non-interventional studies, at least one reaction should have a fatal outcome if the ICSR is serious and with the seriousness criteria ‘Results in death’ applies Any ICSR submitted to EVPM with at least one reaction with the outcome ‘Fatal’ should be classified as serious with a seriousness criterion ‘Result in death’. This validation does not apply to EVCTM 	<ul style="list-style-type: none"> Consistency check between the report seriousness criteria and reaction outcome Identification of fatal reactions
	<ul style="list-style-type: none"> Seriousness criteria should match with the ICSR seriousness 	<ul style="list-style-type: none"> Consistency check between the seriousness of the report and the seriousness criteria of the report

NEW VALIDATION RULES

Validation outcome	Description	Objectives
	<ul style="list-style-type: none"> At least one drug in the report should be 'suspect' or 'interacting' 	<ul style="list-style-type: none"> Identification of suspected or interacting drug(s)
	<ul style="list-style-type: none"> No follow-up report can be submitted for cases which have been previously nullified. An error message will be generated for any additional follow-up report submitted for this case 	<ul style="list-style-type: none"> To avoid re-use of the worldwide unique case identification number once it has been nullified
	<ul style="list-style-type: none"> For any transmission to the EudraVigilance Clinical Trial Module, <ul style="list-style-type: none"> The 'Study name' data element should contain: <ol style="list-style-type: none"> For SUSARs originating in the EEA: <ul style="list-style-type: none"> 'Valid EudraCT Number#Study abbreviated name', For SUSARs originating outside the EEA: <ul style="list-style-type: none"> 'Valid EudraCT Number#Study abbreviated name' or '#Study abbreviated name' Relatedness of Drug to Reaction(s)/Event(s) (<i>ICH E2B(R2) B.4.k.18</i>) for the suspect/interacting medicinal product(s) should be populated for any reported event/reaction Any initial report of a case, which does not contain at least one reaction having a reasonable causal relationship to at least one of the reported medicinal products considered suspect or interacting, is not accepted in EVCTM 	<ul style="list-style-type: none"> Identification with the EurdraCT Number of the interventional clinical trial in which the SUSAR(s) originated for interventional clinical trials authorised in the EEA Distinction of adverse reactions related to the suspected/interacting medicinal product(s) from other events/reactions unrelated to the suspected/interacting medicinal product(s)

NEW VALIDATION RULES

Validation outcome	Description	Objectives
	<ul style="list-style-type: none"> Any report from study transmitted to the EudraVigilance Post-Authorisation Module, should have the data element 'Study type' populated with 'individual patient use' or 'other studies' 	<ul style="list-style-type: none"> Differentiation of spontaneous reports from reports originating in non-interventional studies
	<ul style="list-style-type: none"> The 'Test Name' data element should be populated with a valid lower level term (LLT) MedDRA term or code 	<ul style="list-style-type: none"> Standardisation of reported test name
	<ul style="list-style-type: none"> Only numeric LLT MedDRA codes should be used in designated fields (except in the data element 'Test Name' where valid LLT MedDRA terms are also accepted) 	<ul style="list-style-type: none"> Standardisation of reported data
	<ul style="list-style-type: none"> Values of age, weight and height should not be above 150 years, 650 kg and 250 cm respectively 	<ul style="list-style-type: none"> Data quality control
	<ul style="list-style-type: none"> All dates except the message date and the transmission date of the ICSR should be inferior or equal to the date of receipt of the most recent information EudraVigilance Gateway date 	<ul style="list-style-type: none"> Data quality control
	<ul style="list-style-type: none"> All start dates should be inferior or equal to their corresponding end dates 	<ul style="list-style-type: none"> Data quality control
	<ul style="list-style-type: none"> All dates (including imprecise dates) should not be in the future 	<ul style="list-style-type: none"> Data quality control

NEW VALIDATION RULES

Validation outcome	Description	Objectives
Classified as “warning” in case of non compliance	If the data element ‘Pharmaceutical form (Dosage form)’ is populated, the value should match with the latest version of the European Pharmacopoeia Pharmaceutical Forms list. See http://eudravigilance.emea.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp or http://eudravigilance.ema.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp	<ul style="list-style-type: none"><li data-bbox="1263 432 1711 459">• Standardisation of reported data

Annex 2: Technical instructions on the implementation of the new domain name

1. Instructions for all sending messages to EudraVigilance:

Many of the Agency's systems have already been changed to use the new domain name ".ema" instead of ".emea". These instructions describe the changes you need to make to your systems so that safety reports can be sent to the Agency following the implementation of this new domain name EudraVigilance. This domain name change coincides with the introduction of the new business rules for safety reports². This implies the following:

1.1. On 3 November 2010 at 09.00 AM (GMT)

- The EudraVigilance Pre-Production Environment (also known as "EudraVigilance Test Environment") will support the new domain name. This will affect both safety report messages and product messages. Safety report messages (ICSRs/SUSARs) which reference the old domain (in the XML header) will be validated against the old business rules and safety report messages which reference the new domain will be validated against the new business rules. The product messages (EVPRMs) contain a reference to an XML schema rather than a DTD.
- EVPRM messages will be processed in the same way regardless to which domain name / schema is specified in the header because no changes are being made to the rules affecting these messages.
- Organisations will be able to use the EudraVigilance Pre-Production Environment from 09.00 AM on 3 November 2010 to test the system changes relating to the new business rules and the new domain name.
- No changes will be made to the production environment on this date. Any messages sent to the production environment at this time referencing ".ema" will be rejected.

1.2. On 7 February 2011 at 09.00 AM (GMT)

- EudraVigilance Pre-Production Environment and the EudraVigilance Production Environment will ONLY support the new domain name. Messages that reference the old domain (.emea) in the XML header will be rejected.

1.3. Schedule

DATES	DOMAINS SUPPORTED	BUSINESS RULES SUPPORTED
3 November 2010	External Test: EMEA	Old business rules
	External Test: EMA	New business rules
	Production: EMEA	Old business rules
7 February 2011	EMA ONLY	New business rules ONLY

² Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs), EMA/H/20665/04/Final Rev. 2 (October 2010)

2. Instructions concerning the XML files generated by your systems

2.1. DTDs for ICH E2B(R2) XML files

Your software must be modified to generate ICH E2B(R2) XML files that refer to the DTDs on the new domains. In particular:

- `<!DOCTYPE ichicsr SYSTEM ""http://eudravigilance.emea.europa.eu/dtd/icsr21XML.dtd">`

Must be changed to:

- `<!DOCTYPE ichicsr SYSTEM ""http://eudravigilance.ema.europa.eu/dtd/icsr21XML.dtd">`

2.2. DTDs for ICH E2B(R2) Acknowledgment files

Your software must be modified to generate ICH E2B(R2) Acknowledgment files that refer to the DTDs on the new domains. In particular:

- `<!DOCTYPE ichicsrack SYSTEM
"http://eudravigilance.emea.europa.eu/dtd/ichicsrack11XML.dtd">`

Must be changed to:

- `<!DOCTYPE ichicsrack SYSTEM
"http://eudravigilance.ema.europa.eu/dtd/ichicsrack11XML.dtd">`

2.3. XSD for EVPRMs

Your software must be modified to generate EVPRMs that refer to the XSDs in the new domains. In particular:

- `<evprm XMLns="http://eudravigilance.emea.europa.eu/schema/euevmpd"
XMLns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xsi:schemaLocation="http://eudravigilance.emea.europa.eu/schema/euevmpd
http://eudravigilance.emea.europa.eu/schema/euxevmpd.xsd">`

Must be changed to:

- `<evprm XMLns="http://eudravigilance.ema.europa.eu/schema/emaevmpd"
XMLns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xsi:schemaLocation="http://eudravigilance.ema.europa.eu/schema/emaevmpd
http://eudravigilance.ema.europa.eu/schema/emaxevmpd.xsd">`

We strongly recommend that you test the above modifications to your system by sending several messages to the EudraVigilance Pre-Production Environment.

3. Instructions on how to deal with XML files referring to the emea.europa.eu domain:

XML files (ICSRs, Acks, EVPRMs) that refer to the emea.europa.eu domain will no longer be usable from 7 February 2011 09.00 AM GMT, unless the reference to emea.europa.eu is replaced with ema.europa.eu as described above.

EMA will process all legacy files that are stored in the EudraVigilance database to replace the reference to emea.europa.eu with ema.europa.eu. The original files, as submitted by you, will be stored offline for legal purposes.

If you are locally storing files that refer to the emea.europa.eu domain and will need to use those from 7 February 2011 09.00 AM GMT, you are advised to convert your files to refer to the ema.europa.eu domain. A tool that can assist you in this will shortly be available on the EudraVigilance website. A separate communication will be issued advising you of the location.

4. Instructions for EVWEB users only:

The URL to access EVWEB Pre-Production Environment will change to

<http://evtest.ema.europa.eu>

and the EVWEB Production Environment will change to:

<http://eudravigilance.ema.europa.eu>

The EVWEB Production Environment will start generating XML files referring to the new domain name at 09.00 AM (GMT) on the 7 February 2011. The validation of the safety messages will also be based on the new business rules for safety reports³.

Any files in your WebTrader Archives will be automatically converted on 7 February 2011. However, if you have downloaded any of your XML submissions to your local IT network/local PC you will need to convert these files to be able to view and use these saved files.

A conversion tool will be made available at the EudraVigilance website (see section EudraVigilance Technical Documents) to assist you in doing this.

5. E2B(R2) DTD conversion tool:

5.1. Introduction

The conversion tool is a simple visual basic program that will make a copy of any XML E2B(R2) ICSR files or EVPRMs in a selected directory and convert the DTD/XSD reference from the old DTD/XSD reference to the new DTD/XSD reference.

Minimum system Requirements: Microsoft windows XP, Vista or 2000.

5.2. Recommendations

It is recommended that you only use this program on copies of any XML E2B(R2) ICSR or EVPRMs files that you wish to convert.

5.3. Instructions

1. Unzip the file to a suitable location on your computer;
2. Double click on the program file to run;
3. In the application Select the directory where copies of your XML E2B(R2) ICSR or EVPRMs files are kept;

³ Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs), EMA/H/20665/04/Final Rev. 2 (October 2010)

4. Press the Convert files button;
5. All XML files will be copied and will have the suffix "_New Domain" added to their file names, these converted files will then have the new DTD reference.

5.4. Disclaimer

This conversion tool is provided for free to use, however the EMA will take no responsibility for any loss of data that may occur during its use.

By using this conversion tool, you assume all risks associated with the use of this conversion tool, including any risk to your computer, software or data being damaged by any virus, software, or any other file, which might be transmitted or activated by it. The EMA shall not in any event be liable for any direct, indirect, punitive, special, incidental, or consequential damages, including, without limitation, lost revenues, or lost profits, arising out of or in any way connected with the use or misuse of the tool.

6. Instructions for EudraVigilance trainees only:

The URL to access the EVWEB Training Environment will be changed to:
<http://evtraining.ema.europa.eu> at 09.00 AM (GMT) on 7 February 2011

7. Frequently asked questions

7.1. When can an organisation start using the new business rules?

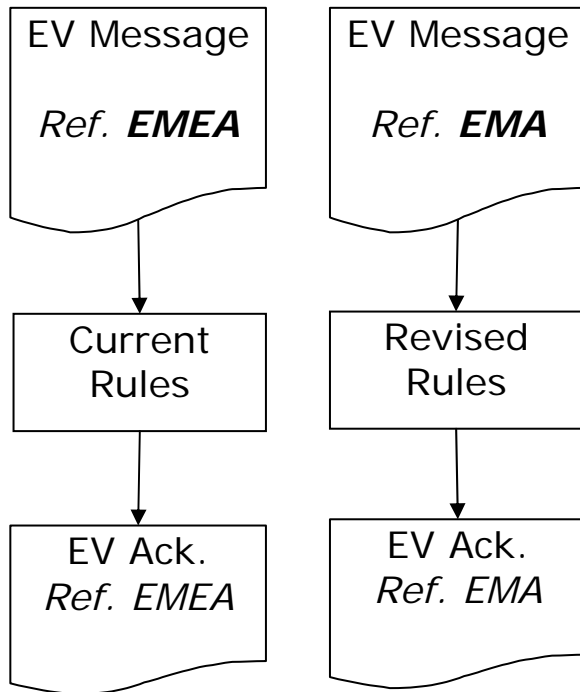
When creating messages, these can be made compliant with the new rules immediately as the new rules are stricter than the old rules. Messages must not be rejected based on the new rules until 09.00 AM (GMT) on 7 Feb 2011.

7.2. Can an organisation test the new business rules before changing to use the new domain name?

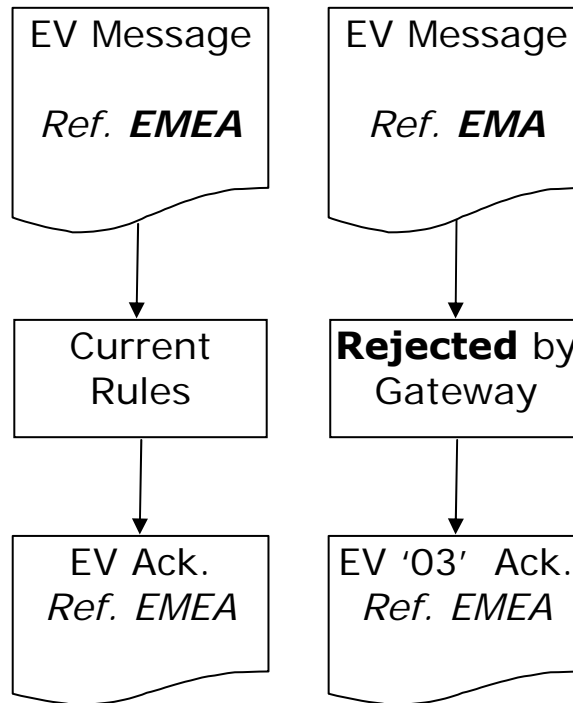
Yes, by loading XML files into EVWEB or by manually changing the header of the XML file and use the EudraVigilance Post Function capabilities within the Test environment from 09.00 AM (GMT) on 3 November 2010.

Annex 3 Technical implementation of the new domain name and revised Business Rules

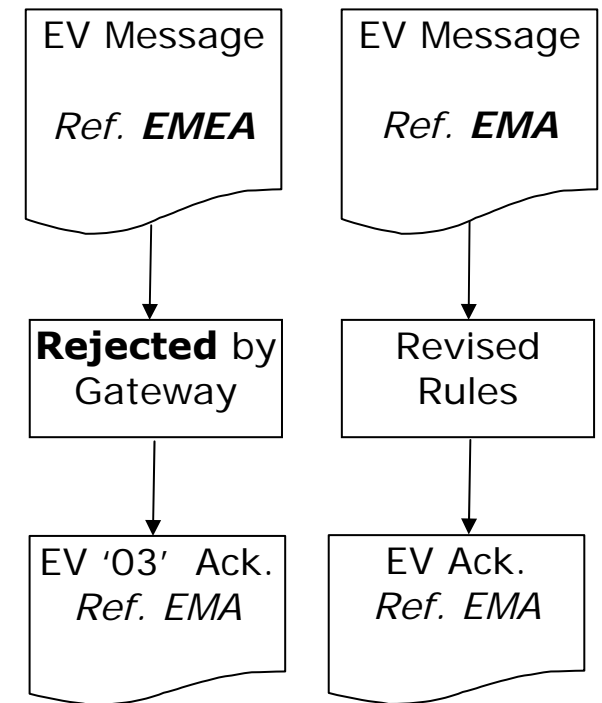
03 Nov. 2010



03 Nov. 2010



07 Feb. 2011



Pre-production (Test) environment

Production environment

Pre-production (Test) environment & Production environment