

Information sheet

Guidance for Industry on the electronic exchange of ICSRs in E2B(R2) format through PV Gateway

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1 Introduction

This guidance intends to assist all marketing authorization holders (MAHs) in preparing the electronic transmission of Individual Case Safety Reports (ICSRs) in pharmacovigilance. This document discusses general issues related to the electronic transmission of ICSRs, with the goal of achieving common standards, for a successful electronic exchange of ICSRs.

Swissmedic supports the electronic transmission of ICSRs. In developing its electronic reporting systems Swissmedic has the ability to generate and receive electronic reports that comply with the ICH standards.

The electronic reporting requirements apply to all MAHs which do have ICH-E2B compliant pharmacovigilance systems.

For companies which do not fulfil the conditions to introduce an exchange of ICSRs via the B2B-Gateway, the electronic reporting system EIViS (Electronic Vigilance System) will be kept on the midterm. You may find further details about EIViS on the Swissmedic website (www.swissmedic.ch).

2 Goal

This guideline stipulates the requirements for MAHs to participate in E2B electronic exchange of ICSR between Swissmedic and MAHs (bidirectional) and provides guidance on the technical and procedural standards applied by Swissmedic.

3 Scope

MAHs are obliged by law to report certain ICSRs to Swissmedic and Swissmedic forwards ICSRs received from other sources to concerned MAH. The scope of this guideline covers Swissmedic and all MAH for products marketed in Switzerland.

4 General Principles / Information

4.1 Electronic exchange / reporting of ICSRs

Electronic transmission of ICSR is a two-way process, which affects only the reporting mechanism. The legal reporting requirement does not change (see TPA Art. 58, 59 and TPO Art. 61-66). According to the legislation the MAHs are required to submit the following Individual Case Safety Reports (ICSRs) referred also as safety reports to Swissmedic:

- all spontaneous Swiss serious ICSRs
- all spontaneous Swiss non-serious unexpected ICSRs including ICSRs from observational / non-interventional Studies, PASS, registries, compassionate use etc.
- abuse
- medication errors and “near miss” on individual bases with focus on risk minimization possibility
- lack of effect according to the international standard (vaccines, contraceptives, biological etc.)

This note for guidance does currently not address:

- SUSARs (suspected unexpected serious adverse reactions reports) from at Swissmedic notified Interventional Clinical Trials.

A valid ICSR for reporting to Swissmedic must fulfil the four minimum reporting criteria: an identifiable reporter, an identifiable patient, a reaction and a suspected medicinal product.

For anonymization of the case report the EMA rules should be applied (see chapter 10.2).

The complete information for an ICSR that is available to the sender should be reported in the structured fields and in the narrative. Any supporting information related to the case must be sufficiently described within the ICSR and should be listed in section A.1.8.2 (document list), A.2.2 (literature reference) or the narrative (B.5.1). See chapter 10.2.

For ICSR arising from literature, the adequate/correct reference must be placed in the section A.2.2 (literature reference). The article itself must be submitted by mail to vigilance@swissmedic.ch attached as a separate PDF document.

In addition, whenever more recent important information on an individual case is submitted, (e.g. follow-up information, ICSR highlighted for nullification) the complete (entire) information on the case has to be provided and not only partial information e.g. changes or updates.

For those ICSRs that are highlighted for nullification (‘Report nullification’, A.1.13, set to ‘yes’) also the reasons for nullification must be indicated, see chapter 10.2.

4.2 Important Notes

MAHs are advised to reduce the number of follow-ups to a minimum; only new and medical relevant information such as outcome, alternative medical conditions, other suspect drugs, results of performed investigations or any other data with impact on causality should initiate follow-up information. Ideally an initial case should be followed by one follow-up, at the time of case closed.

Further information on the current reporting obligations can be found on the Swissmedic homepage under FAQs on General Pharmacovigilance: [FAQs: General Pharmacovigilance \(swissmedic.ch\)](https://www.swissmedic.ch/faq-general-pharmacovigilance)

4.3 The Swissmedic PV System and ICH Guidelines

Vigilance One Ultimate, the Swissmedic Pharmacovigilance System, is designed on top of the E2B format with the aim of being E2BR3 compatible. Therefore no major difficulties regarding E2B interpretation are expected.

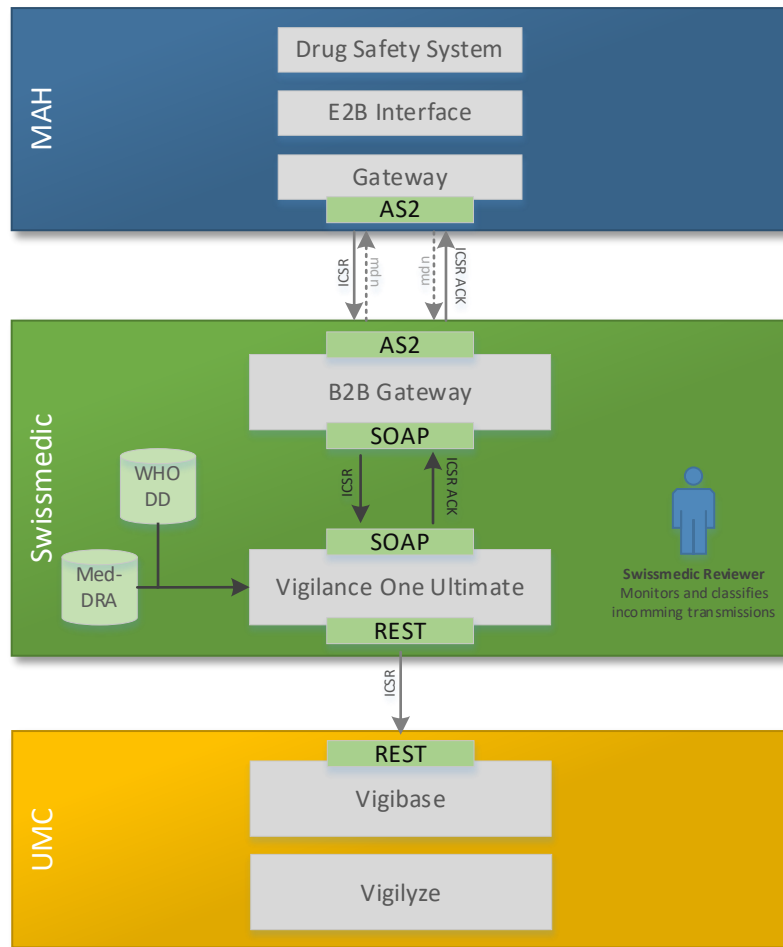
Safety and acknowledgement messages have to follow the content and format of the respective ICH guidelines:

- Data Elements for the Electronic Transmission of Individual Case Safety Reports' version 4.4.1 dated 5 February 2001, see chapter 10.2
- Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1). Document Revision February 2001, see chapter 10.2

5 Processing of safety reports (ICSRs)

Vigilance One Ultimate, the Swissmedic PV system has the ability to generate and receive electronic reports that comply with the ICH standards as detailed in E2B (M). The following chapter describes the processing and management of safety reports and some important standard procedures.

5.1 PV System Overview



5.2 Import

It is important that MAHs comply with the below listed checks when submitting electronic ICSRs to ensure that reports are not automatically rejected (negative ACK-Log) by the system.

- In a first step the drug safety system checks each incoming file if:
 - the incoming file is a valid xml file (as defined by W3C)
 - the safety message is in accordance with the ICH ICSR Document Type Definition (DTD), see chapter 10.2.
 - the sender information is complete (the fields “sender information”, “sender organization” and “sender identifier”).

2. In a second step the drug safety system checks each safety report for:

- field lengths
- lexicon / dictionary values
- a missing safety report id
- the worldwide unique number (rejects initial if it is missing or if both authoritynumb and company numb are filled in)
- a missing report type

The Swissmedic PV System accepts MedDRA terminology and WHO-Drug Dictionaries.

5.3 Export

The Swissmedic PV system uses the MedDRA terminology (for ex. Indications, reactions, etc).

In order to be able to comply with the revised EMA business rules in preparing and processing ICSRs, a validation tool based on the EMA business rules is implemented in Vigilance One Ultimate (see chapter 10.2).

The exported files are checked against the EMA business rules (see chapter 10.2). Some fields however cannot be validated or are not of relevance.

The table below outlines these exceptions:

E2B (R2) - field	name	comments
N/A	'EudraVigilance Gateway date'	Not relevant
M.1.5 M.1.6 A.3.1.2 A.3.2.2a	messagereceiveridentifier messagesenderidentifier senderorganization receiverorganization	The SM identifier may not correspond to the EMA identifier list.
A.1.	reporttype	Not relevant
A.2.1.2e A.2.1.2	reporterstate reporterpostcode	Not relevant
A.2.3.1 A.2.3.2	studyname sponsorstudynumb	Not relevant
A.3.2.	receivertype	Not relevant
B.1.7.1a.1 B.1.8f.1 B.1.8g.1 B.1.9.2a B.1.9.4a	patientepisodenamemeddraversion patientindicationmeddraversion patientdrgreactionmeddraversion patientdeathreportmeddraversion patientdetermautopsmeddraversion	

E2B (R2) - field	name	comments
B.1.10.7.1a.1 B.1.10.8f.1 B.1.10.8g.1 B.2.i.1.a B.2.i.2.a B.4.k.11a B.4.k.17.2a B.5.3a B.4.k.18.1a	parentmdepisodemeddraversion parentdrgindicationmeddraversion parentdrgreactionmeddraversion reactionmeddraversionllt reactionmeddraversionpt drugindicationmeddraversion drugrecuractionmeddraversion senderdiagnosismeddraversion drugreactionassesmeddraversion	
B.1.7.1a.2 B.1.8f.2 B.1.8g.2 B.1.9.2.b B.1.9.4b B.1.10.7.1a.2 B.1.10.8f.2 B.1.10.8g.2 B.2.i.1.b B.2.i.2.b B.3.1c B.4.k.11b B.4.k.17.2b B.5.3b B.4.k.18.1b	patientepisodename patientdrugindication patientdrugreaction patientdeathreport patientdetermineautopsy parentmedicalepisodename parentdrugindication parentdrugreaction reactionmeddrallt reactionmeddrapt testname drugindication drugrecuraction senderdiagnosis drugreactionasse	
B.1.8a B.1.10.8	patientdrugname parentdrugname	The SM safety system uses the WHO drug dictionary which does not correspond to the EMA medicinal products list. Furthermore free text is allowed.
B.4.k.2.1	medicinalproduct	The SM safety system uses the WHO drug dictionary which does not correspond to the EMA medicinal products list. Furthermore free text is allowed and this field is not mandatory (as well as B.4.k.2.2) in the SM safety system.
B.4.k.2.2	activesubstancename	The SM uses the WHO drug dictionary which does not correspond to the EMA medicinal products list. Furthermore free

E2B (R2) - field	name	comments
		text is allowed and this field is not mandatory (as well as B.4.k.2.1) in the SM safety system which will most likely not affect the companies since Swissmedic will check that field.
B.4.k.7	drugdosageform	Not relevant
B.4.k.18.2	drugassessmentsource	Not relevant
B.4.k.18.3	drugassessmentmethod	The SM safety system places “WHO causality” into these fields (provided as free text).
B.4.k.18.4	drugresult	The WHO causality is provided as free text.

6 Starting electronic submission

Before the electronic transmission of ICSRs can be initiated, the MAHs should follow the steps as indicated below.

6.1 Send letter of intent

A Letter of Intent for the Electronic Transmission of ICSRs must be sent to the PV Specialist (Process Specialist) at Swissmedic (see conditions on www.swissmedic.ch).

The Process Specialist will then contact the MAH to plan a time period for a Gateway setup.

6.2 Test Phase

During the test phase the currently established regulatory reporting mechanism remain unaffected. It is recommended that the MAH keeps a copy of configuration settings including certificates (public key) used during the test phase to enable the MAH to reconstruct the identical test environment for subsequent testing at a later stage.

6.2.1 PV system compatibility test

For the tests the MAH and Swissmedic need to exchange and load the following XML test files into the drug safety system to check whether the E2B structure and the validation rules will work

- an initial report (including medical and drug history)
- a follow-up report
- a parent child report
- a non-interventional (observational) study report
- a case reported in the literature
- a nullified / duplicate report (A.1.11; A.1.13) completed, see chapter 10.2

6.2.2 B2B-Gateway connection process

After configuration of the Gateways (Swissmedic and MAH), it is necessary to test whether the Gateways can communicate (technical layer AS2). It is tested if the party's Gateway is interoperable with the Swissmedic Gateway. Senders may have to adopt hardware, software and data communication configurations to meet the recommended communication standards.

The first of three steps to connect to the B2B-Gateway is the (1) system integration and test (test environment), (2) is the system configuration and end to end test between the drug safety systems (test environment) and finally (3) the system configuration and pilot (productive environment).

6.2.3 Exchange certificates

Swissmedic is not mandating any particular software for the electronic communication of ICSRs. If party's software is fully interoperable with the Swissmedic Gateway, then the sender will receive certification from Swissmedic to use it. Swissmedic also needs the public certificate of each participating MAH.

6.3 Operational phase

Following successful completion of the operational test phase, the operational phase is initiated when electronic transmission of ICSRs replaces the currently established regulatory transmission between the parties.

6.4 Contingency plan

6.4.1 Malfunction Electronic Pharmacovigilance System Swissmedic

When Swissmedic detects malfunction of the electronic Pharmacovigilance System (database and/or gateway), Swissmedic investigates the root cause for system failure and carries out a preliminary estimation of expected system downtime within a maximum of 24 hours after detection of system malfunction. Two scenarios are used:

Scenario B

If system downtime is estimated to be equal to or less than 5 calendar days, the Swissmedic informs concerned MAH by e-mail that the electronic Pharmacovigilance System is expected to be out of service for a maximum of 5 calendar days and that electronic case submission is delayed. Concerned MAH will be informed by a separate e-mail to the same e-mail once the system is up and running again. The situation is continuously monitored and if after 4 business days it is deemed unlikely, that the system is up and running again after 5 days the failure is changed to scenario A. Swissmedic uses medical judgement to identify cases deemed critically important for processing under scenario A.

Scenario A

If system downtime is estimated to be more than 5 days, cases fulfilling the Swissmedic criteria for expedited reporting are sent via FileShare in E2B XML file format.

6.4.2 Malfunction Electronic Pharmacovigilance System MAH

When a MAH detects malfunction of the electronic Pharmacovigilance System (database and/or gateway), the MAH investigates the root cause for system failure and carries out a preliminary estimation of expected system downtime within a maximum of 24 hours after detection of system malfunction. Two scenarios are used:

Scenario B

If system downtime is estimated to be equal to or less than 5 calendar days, the MAH informs Swissmedic by e-mail to pvgateway@swissmedic.ch that the electronic Pharmacovigilance System is expected to be out of service for a maximum of 5 calendar days and that electronic case submission will include all cases not successfully sent before (ack-log received from Swissmedic). Swissmedic will be informed by a separate e-mail to the same e-mail once the system is up and running again. The situation is continuously monitored and if after 4 business days it is deemed unlikely, that the system is up and running again after 5 days the failure is upgraded to scenario A. The MAH uses medical judgement to identify cases deemed critically important for processing under scenario A.

Scenario A

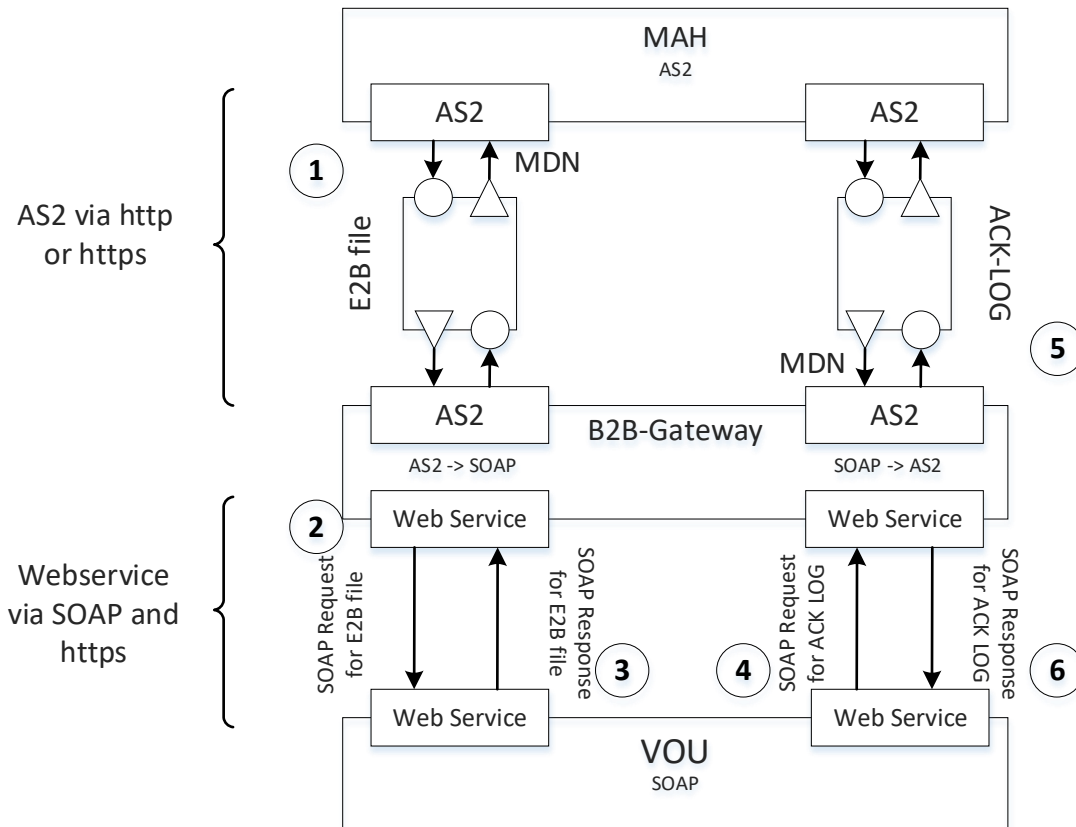
If system downtime is estimated to be more than 5 days, cases fulfilling the Swissmedic criteria for expedited reporting can be sent via FileShare in E2B XML file format. In this case, please contact Swissmedic via pvgateway@swissmedic.ch to initiate the necessary steps for data exchange via this channel. The MAH will assign a provisional case ID and will keep track of this number and will provide the worldwide unique case identifier once the primary pharmacovigilance system is up and running again.

7 Description of the Swissmedic Gateway

The Swissmedic Gateway follows the ICH M2 Gateway Recommendation for the Electronic Transfer of Regulatory Information (see chapter 10.2).

7.1 Communication Overview and process

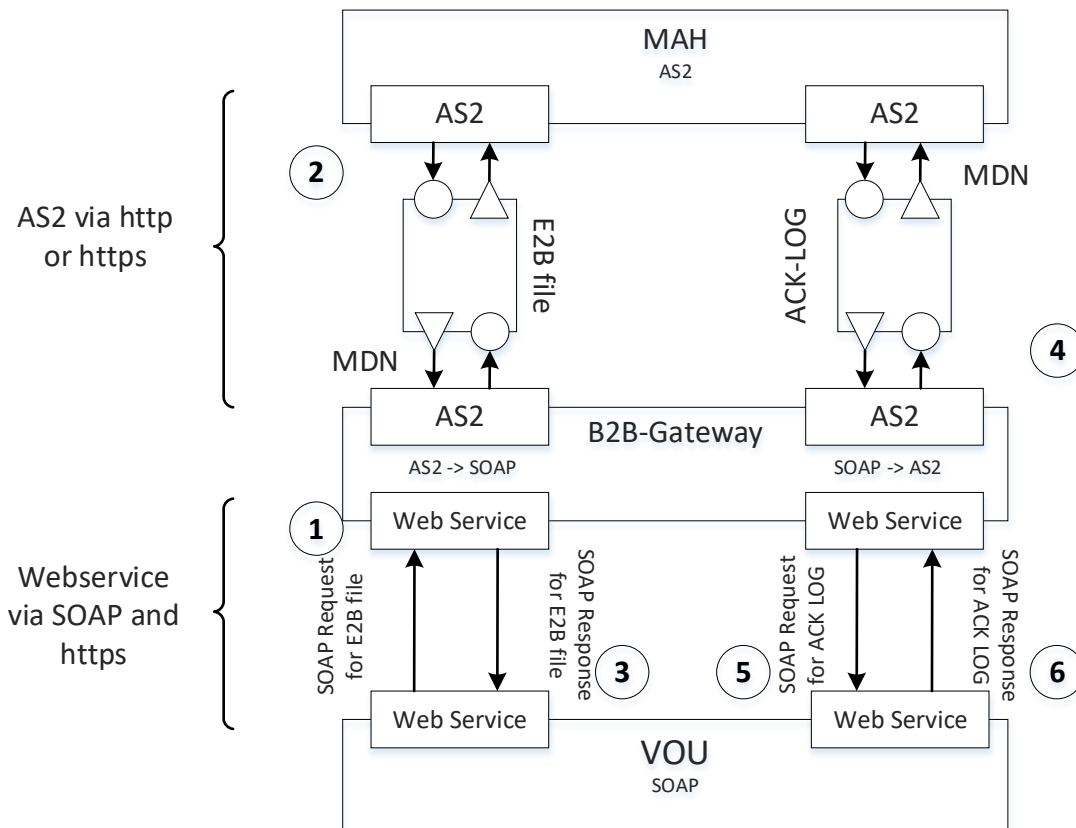
7.1.1 Process MAH transmits E2B to Swissmedic



- 1: MAH transmits an E2B-file to the B2B-Gateway via HTTP/S per AS2 HTTP interface (AS2 quits with MDN)
- 2: The B2B-Gateway forwards the E2B-file to VOU via WEB-service (SOAP request)
- 3: VOU answers via SOAP response to the B2B-Gateway.
- 4: VOU transmits an ACK-LOG to the B2B-Gateway via WEB-service (SOAP Request).
- 5: The B2B-Gateway forwards the ACK-LOG to the accordant MAH. Whether via HTTP/S per AS2 HTTP interface (AS2 quits with MDN)
- 6: The B2B-Gateway answers via SOAP response to VOU.

The B2B-Gateway stores the MDN temporarily on the file-system (90 days). After 90 days the MDN's will be stored for 10 years on a storage system.

7.1.2 Process Swissmedic transmits E2B to MAH



1. VOU transmits an E2B-file to a MAH via WEB-Service (SOAP Request) to the B2B-Gateway.
2. The B2B-Gateway forwards the E2B-file to the accordant MAH via HTTP/S per AS2 HTTP interface (AS2 quits with MDN)
3. The B2B-Gateway answers via SOAP response to VOU.
4. The MAH, who received the E2B-file, transmits an ACK-LOG to the B2B-Gateway via HTTP/S per AS2 HTTP interface (AS2 quits with MDN)
5. The B2B-Gateway forwards the ACK-LOG via WEB-service (SOAP request) to VOU.
6. VOU answers via SOAP response to the B2B-Gateway.

The B2B-Gateway stores the MDN temporarily on the auf file-system. The MDN will be deleted within 90 days. After 90 days the MDN's will be stored for 10 years on a storage system.

7.2 Additional Information

7.2.1 Operational requirements to communicate with the Swissmedic Gateway

Each party must provide, all the equipment, software and services necessary to create, transmit, receive, translate, record and store safety, acknowledgement and MDN messages in compliance with the respective ICH standards and the requirements as defined in this Guidance.

7.2.2 Security Aspects

To facilitate the secure transmission of safety and acknowledgement messages over the Internet, each party has to purchase, install and operate applications that allow for the successful transmission and receipt of encrypted and digitally signed safety and acknowledgement messages via the Swissmedic Gateway.

The applications chosen by each party must provide the essential functionality and interoperability as outlined in chapter 6.

Encrypting and digitally signing safety and acknowledgement messages by using certificates provides the parties assurance about each transaction.

7.2.3 Acknowledgments and error codes

The code of the negative ACK-LOG is `<reportacknowledgmentcode>02</reportacknowledgmentcode>`. The ACK-LOG file will contain a free text field `<errormessagecomment>` with a description of the problem.

8 Information to connect the Swissmedic B2B-Gateway

8.1 General Information

The following section provides information on the organizational and technical framework of Swissmedic and lists the information MAHs must provide to Swissmedic in order to set up a Gateway connection between MAHs and Swissmedic. It also lists the contact persons at Swissmedic.

8.2 Swissmedic

National Competent Authority address	Swissmedic Hallerstrasse 7 3012 Bern Switzerland
PV Specialist (Process Specialist) contact	Swissmedic Name: Manuela Zwahlen E-Mail: manuela.zwahlen@swissmedic.ch
Technical contact	Swissmedic Name: Petya Borissov E-Mail: pvgateway@swissmedic.ch

8.2.1 MAH Certificate test and production

Please send us your certificate to the following e-Mail address: pvgateway@swissmedic.ch

Attention: It is not allowed to provide self-signed certificates!

Note: The provided Data will be used to setup a partner configuration on the B2B-Gateway, e.g. "Require Signature = Yes" means that the B2B-Gateway will sign the messages to MAH.

Time to Acknowledge: The time that the MAH has to acknowledge the reception of a message via a MDN.

After the „Time to Acknowledge“ passed, the message will be resent as often as needed, the delay corresponds to the „Time to Acknowledge“.

9 Basic conditions

9.1 Timeframes

The time conditions are acting in accordance to the used standards within Switzerland (CET).

9.2 Location

The services will be adduced within the premises of the accordant participant.

- PharmApp Solutions GmbH, Erkrath, Germany
- FOITT, Bern, Switzerland
- Swissmedic, Bern, Switzerland
- MAH, MAH city, MAH country

10 Utilities & Equipment

10.1 Equipment

- Phone
- Functional Mail account B2B-Gateway Swissmedic pvgateway@swissmedic.ch
- E-Mail-Client
- Internet portal and actual information. The URL will be communicated to all parties during MAH-coordination meeting

10.2 Relevant documents

- E2B(R2) ICSR Specification and Related Files: [ICH Official web site : ICH](#) (accessed 03.01.2024)
- DTD 2.1; https://admin.ich.org/sites/default/files/inline-files/ich-icsr-v2_1_dtd.zip
- [Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports \(ICSRs\)](#), containing the EMA business rules: (accessed 17.04.2013)

11 Glossary

ACK-Log	Acknowledgment Log. Automatically by receiver generated receipt in after uploading an E2B into the Drug Safety System or Vigilance One Ultimate
ADR	Adverse Drug Reaction
AS2	Applicability Statement 2 (AS2)
E2B	Electronic to Business - ICH Standard for electronic transmission of adverse drug reactions in XML format
EMA	European Medicines Agency
FOITT	Federal Office of Information Technology, Systems and Telecommunication
HP QC	Hewlett Packard Quality Centre
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
ICSR	Individual Case Safety Report
Local Company Number	Internal case number MAH
MAH	Marketing Authorization Holder
MAH type 1	Marketing Authorization Holder with own Gateway
MDN	Message Disposition Notification. Standard receipt AS2 communication
NCA	National Competent Authority
PASS	Post Authorization Safety Study
PI	Product Information
RPVZ	Regional Pharmacovigilance Centre
SM/SMC	Swissmedic
UMC	Uppsala Monitoring Centre
Vigilance One Ultimate (VOU)	System to manage adverse drug reactions used by Swissmedic
WHO	World Health Organisation
WHO-Art	WHO Adverse Reaction Terminology
WHO-Drug	WHO-Drug Dictionary
XML	Extended mark-up language

Change history

Version	Change	sig
6.0	Title of the document has been adapted	stt, zma
5.0	Minor adjustments and updating of illustrations	bop, sgu, stt, vto, zma
4.0	Link to EIViS Guidance integrated, Name of Business responsible person changed, reference to paragraph 12.2 adapted	lc
3.0	<ul style="list-style-type: none"> ▪ Update Graphik PV System overview ▪ Telephone and fax numbers updated ▪ new change history inserted in the document 	lc
2.0	MedDRA Revision	rw
1.0	New document	rw, sgu