

INSTRUCTIONS FOR PHARMACEUTICAL INDUSTRY

Update on electronic transmission of suspected individual case safety reports to the Spanish Medicines and Healthcare Products Agency (AEMPS)

Regulation 726/2004/CE and Directive 2001/83/27/CE amended by Directive 2004/27/CE, established the community procedural for authorization and control of medicinal products. These rules establish the basis to create a network for electronic transmission and pharmacovigilance data exchange between Marketing Authorisation Holders (MAH), and Competent Authorities (CA), including European Medicines Agency (EMA) and Spanish Medicines and Healthcare Products Agency (AEMPS).

The AEMPS has already published two instructions regarding electronic exchange of pharmacovigilance data:

- Electronic transmission of suspected adverse drug reactions to medicinal products of human use to the Spanish Medicines and Healthcare Products Agency (*Agencia Española de Medicamentos y Productos Sanitarios- AEMPS*) (9 de febrero de 2006, v2)
http://www.agemed.es/actividad/documentos/infoInteres/docs/transmi_electronicaRA-feb06.pdf
- Information on electronic transmission of individual case safety reports ("*Orientaciones sobre transmisión electrónica de casos individuales de reacciones adversas*") (27 de julio de 2004)
http://www.agemed.es/actividad/documentos/infoInteres/docs/transmision_electronica-RA.pdf

This document solely refers to ICSRs (Individual Case Safety Reports) occurring in post-authorisation. Therefore, the document is not applicable to suspected adverse reactions occurring in clinical trials (SUSARs), with independence of involved suspected drug.

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ELECTRONIC EXCHANGE OF SUSPECTED ADVERSE REACTIONS REPORTS (ICSRs)

According to Volume 9A¹ and once the Royal Decree 1344/2007 has come into effect (superseding the Royal Decree 711/2002), electronic transmission will become the only means of communicating individual case safety reports (ICSRs).

The AEMPS will initiate contact with pharmaceutical companies who have requested electronic transmission testing. In the near future, a deadline will be released for adapting to the new scenario on electronic transmission.

Marketing Authorisation Holder (MAH) will electronically send ICSRs occurring in Spain to a single point. The database FEDRA will deliver the report to the concerned Pharmacovigilance Regional Centre (CAFV) for validation, evaluation and final data entry. MAH will not need to duplicate delivery to the AEMPS and to the concerned Pharmacovigilance Regional Centre.

In order to facilitate electronic transmission to MAHs, the AEMPS has developed two functionalities in FEDRA to electronically submit ICSRs occurring in Spain:

- Online data entry: a web based tool developed for reporting ICSRs. The tool is designed for companies submitting a reduced number of ICSRs. The tool allows secure electronic submission between the AEMPS and MAHs only. Please note that this tool cannot be used to send ICSRs to other EU competent authorities nor EMEA.
- XML transmission: Exchange electronic transmission will be done according to international standards ICH E2B (M), M1, y M2. MAHs can choose from different possibilities for XML electronic transmission. MAHs can develop their own "estri gateway" (ICH M2) where their database will be able to generate and send XML messages. Also note that the EMEA has developed tools to facilitate electronic exchange of ICSRs. "Eudravigilance Web Trader" allows users the message posting function where MAHs can send and receive ICSRs. This tool was designed for companies whose database can generate XML message but do not have the functionality to send XML messages. "EV-Web" functionality is similar to online data entry offered by AEMPS but it also allows electronic exchange with other competent authorities and MAHs.

The AEMPS will communicate to EMEA (Eudravigilance – Post-authorisation Module, referred to as EV-PM) any serious ICSRs occurring in Spain received either through yellow card or pharmaceutical companies according to European legislation (Art. 24 – Regulation 726/2004/CE; Art. 105 – Directive 2001/83/27/CE amended by Directive 2004/27/CE; and Spanish Royal Decree 711/2002).

Serious and unexpected ICSRs occurring outside the EEA with medicinal products marketed in Spain will be submitted by MAHs to the EMEA (EV-PM) within 15 days. Legal submission requirements with the AEMPS will be fulfilled by MAHs with the EMEA submission. The AEMPS does not wish to receive a duplicate submission.

¹ Volume 9 A of the Rules Governing Medicinal Products in the European Union. Guidelines on pharmacovigilance for Medicinal Products for Human Use, version final March 2007. Available on the web: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf

1. ONLINE DATA ENTRY

The AEMPS offers MAHs a secure access through SINAEM portal to enter expedited cases directly into FEDRA. Those reports will be validated and evaluated by the concerned CAFV, according to current legislation.

SINAEM portal provides secure access to AEMPS databases including submission of ICSRs. The portal is a secure environment with an SSL security protocol (<https://sinaem.agemed.es>). Access to SINAEM requires users to install an electronic certificate class 2CA issued by a Certification Authority. In Spain, the Certification Authority is the "Fábrica Nacional de Moneda y Timbre (FNMT)". This electronic certificate can be obtained through Internet (<http://www.fnmt.es>). It is highly recommended to apply for electronic certificates for every person who wishes to access the system to avoid future delays. Companies can choose to apply for individual or corporate electronic certificates to the FNMT. Certificates need to be renewed every 2-3 years.

1.1 Requirements for online data entry

Computers accessing FEDRA through SINAEM should fulfil the following technical requirements:

- Microsoft Windows® NT, Windows® 2000 or Windows® XP
- Microsoft Office® 2000 or Office® XP.
- Internet Explorer® 6.0 with Service Pack 1, with cipher strength 128-bit. Version 6.0 includes this cipher strength 128-bit, maximum level of protection.
- Internet access: it is recommended ADSL con 128 kbps, as minimum band width.
- It is not recommended to use Microsoft Windows Vista or Microsoft Internet Explorer 7.0

1.2 How to request online user access

In order to start online data entry, a user and password will be requested from the Pharmacoepidemiology and Pharmacovigilance Division. The application form should be signed by the legal representative. The form is included as Annex 1 (Annexes are in Spanish only). The form will be addressed to the Pharmacoepidemiology and Pharmacovigilance Division by post, fax or email:

- Postal address: "Registro General". Agencia Española de Medicamentos y Productos Sanitarios, c/ Campezo 1, E-28022 Madrid.
- Fax: +34 91 822 53 36
- E-mail: fvicsr@agemed.es

Once the user has been authorised, access to FEDRA will be through SINAEM portal. A user guide (in PDF, User Guide available only in Spanish) is available from the main menu in FEDRA.

1.3 Sending ICSRs from AEMPS to pharmaceutical companies

AEMPS will send expedited reports to pharmaceutical companies with online access every two weeks by post, as usual.

2. XML TRANSMISSION

FEDRA is fully compatible with EudraVigilance, European system for exchanging ICSRs with the EMEA. Electronic transmission will be made following ICH M2 and through the EMEA gateway. This electronic connection will allow sending more than one ICSR in each XML message.

Pharmaceutical companies will communicate to AEMPS ICSRs occurring in Spain. The AEMPS will send them to EudraVigilance–PM.

2.1. Requirements for XML transmission

Pharmaceutical companies will request from the EMEA two ID-profiles for test and production. Where a MAH intends to transmit on behalf of other companies with a single ID-profile, this should be communicated in writing to the AEMPS. The AEMPS will send ICSRs belonging to the group to the single ID.

In this way, EMEA has assigned the following ID-profiles for AEMPS–Human Pharmacovigilance:

- Test: **AGEMEDT**
- Production: **AGEMED**

When sending ICSRs from pharmaceutical companies, the SENDER will be the company ID-profile while the RECEIVER will be the AEMPS (Human pharmacovigilance) ID-profile, i.e. AGEMED (test ID) or AGEMDT (production ID).

When sending ICSRs from AEMPS, the SENDER will be the AEMPS ID-profile, while the RECEIVER will be the company ID-profile.

A testing phase is required before starting electronic transmission in production. Testing phase is similar to the EMEA testing. An application form should be signed by the legal representative. The form is included as Annex 2 ("*SOLICITUD DE PRUEBAS DE TRANSMISIÓN EN XML CON LA AEMPS*", Annexes are in Spanish only). The form will be addressed to the Pharmacoepidemiology and Pharmacovigilance Division by post, fax or email. AEMPS will contact the responsible person to agree on a timetable for testing.

- Postal address: "Registro General" Agencia Española de Medicamentos y Productos Sanitarios, Campezo 1, E-28022 Madrid.
- Fax: +34 91 822 53 36
- E-mail: fvicsr@agemed.es

Those pharmaceutical companies ready to send ICSRs but not to receive from AEMPS will have to annotate it in the application form. In this scenario, AEMPS will post a paper delivery with those ICSRs received from health professionals through the yellow card scheme, fulfilling expedited reporting requirements to pharmaceutical companies. Bear in mind that this paper delivery will be considered as an electronic transmission and a worldwide unique case identification number (A.1.10.1) will be assigned.

2.2. AEMPS technical requirements for electronic transmission of ICSRs

Field	Field descriptor	Definition	Comments
M.1.5	messagesenderidentifier	Sender	It should be the same as A.3.1.2 field (senderorganization). Both fields should correspond with MAH – Profile ID provided by EMEA. The identifiers will be loaded in a reference table to ensure senders and receivers identification when sending and receiving ICSRs
A.1.1	primarysourcecountry	Primary source country	Only Spain (ES) will be accepted as country for this field. A warning in the acknowledgement receipt will be generated for any ICSRs coming from a different country. Two different warnings will be generated. Where the country is an EEA member other than Spain, the warning will inform the sender to send the ICSR to such country. Where the country is not an EEA member, the warning will inform the sender to send the ICSR to EudraVigilance-PM only.
A.1.5.1	serious	Seriousness	Where the field is blank, a warning will be generated in the acknowledgment receipt.
A.1.5.2	seriousnessdeath/ lifethreatening/ hospitalization/ disabling/ congenitalanomaly/ other	Seriousness criteria	When A.1.5.1 field (serious) is 1 (yes), any of the A.1.5.2 fields should be selected. If none of the field is selected, a warning will be generated in the acknowledgment receipt.
A.2.1.2e	reporterstate	Autonomous Community	At least one field between A.2.1.2e .and A.2.1.2f should be selected. The Autonomous Community (A.2.1.2e) is identified by 19 numerical codes. When A. 2.1.2e does not correspond with the Autonomous Community where the city/town is located, an error message will be generated and the message will be rejected. Autonomous Community coding is as follows: 01 ANDALUCIA 02 ARAGON 03 ASTURIAS 04 ISLAS BALEARES 05 CANARIAS 06 CANTABRIA 07 CASTILLA Y LEON 08 CASTILLA-LA MANCHA 09 CATALUÑA 10 COMUNIDAD VALENCIANA 11 EXTREMADURA 12 GALICIA 13 COMUNIDAD DE MADRID 14 MURCIA 15 NAVARRA

			<p>16 PAIS VASCO</p> <p>17 LA RIOJA</p> <p>18 CEUTA</p> <p>19 MELILLA</p>
A.2.1.2f	reporterpostcode	Reporter postcode	<p>At least one between A.2.1.2e and A.2.1.2f. should be selected. A.2.1.2f should be “the city/towns’ INE code”. This is an alphanumeric code with 6 digits. “The city/towns’ INE code” is considered more useful than postcode because it allows classification by regions and cases will be forward to the concerned Regional Pharmacovigilance Centre. Spanish legislation requests cases to be sent to concerned Regional Pharmacovigilance Centre.</p> <p>Where both fields A. 2.1.2e and A.2.1.2f are filled and A.2.1.2e does not correspond with the Autonomous Community where the city/town is located, an error message will be generated and the message will be rejected.</p>
A.3.1.2	senderorganization	Sender	This field should be the same as M.1.5 (messageidentifier)
A.3.2	receiver		<p>It is not mandatory. If you choose to include it, the information should be as follows:</p> <p>Receiver type = “2”</p> <p>Receiver organization = AEMPS</p> <p>Receiver department = Div. Farmacoepidemiología y Farmacovigilancia</p> <p>Receiver title = Dr.</p> <p>Receiver given name = Mariano</p> <p>Receiver family name = Madurga</p> <p>Receiver street address = C/ Campezo 1</p> <p>Receiver city = Madrid</p> <p>Receiver state = Madrid</p> <p>Receiver postcode = 28022</p> <p>Receiver tel = 918225330</p> <p>Receiver tel country code = 34</p> <p>Receiver fax country code = 34</p> <p>Receiver fax = 918225336</p>
B.1.1	patientinitial	Patient initials	Personal Identification is not allowed under the Spanish Data Protection Law, e.g. initials, name, medical records, Spanish ID (DNI).
B.1		Patient data	At least one between B.1.2.1b, (B.1.2.2a, and B.1.2.2b), (B.1.2.2.1a and B.1.2.2.1b), B.1.2.3, B.1.5.
B.2.i.4b	reactionstartdate	Reaction start date	A warning will be generated where this field is blank. At least year should be stated.
B.2.i.8	reactionoutcome	Outcome	A warning will be generated where this field is blank.
B.3.1c	testname	Test	MedDRA code should be used.
B.4.k.12b	drugstartdate	Drug start date	At least one of the fields B.4.k.12b (drugstartdate) and B.4.k.13a (drugstartperiod) should be filled. Otherwise a warning message will be generated.
B.4.k.13a	drugstartperiod		At least one of the fields B.4.k.12b (drugstartdate) and B.4.k.13a (drugstartperiod) should be filled. Otherwise a warning message will be generated.
B.5	summary		See below section 2.3.1

Note: FEDRA performs a validation of any incoming safety message and an acknowledgement message will be returned to the sender with the results of the outcome of the loading process and any detected *errors* and *warnings*: where an *error* is generated the report will not be loaded into the database due to non-compliance with business rules; where a *warning* is generated, the report will be loaded, but pending information should be sent as soon as possible.

2.3. Other requirements for electronic transmission

2.3.1 Language

The following E2B fields should be in Spanish or in English or both when possible. The original reporter verbatim should always be clearly stated.

A.1.8.1	List of documents held by sender
A.1.13.1	Reason for nullification
A.2.3.1	Study name
B.1.7.1g	Relevant medical history and concurrent conditions: Comments
B.1.7.2	Text for relevant medical history and concurrent conditions
B.1.10.7.1g	Relevant medical history and concurrent conditions of parent: Comments
B.1.10.7.2	Text for relevant medical history and concurrent conditions of parent (not including reaction)
B.2.i.0	Reaction as reported by primary source
B.3.2	Results of test and procedures relevant to the investigation of the patient
B.4.k.6	Drug Dosage text
B.4.k.19	Additional information on drug
B.5.1	Case narrative (see note below)
B.5.2	Reporter's comment
B.5.4	Sender's comments

Field B.5.1 *Case narrative* will include a short description of the case in both Spanish and English.

2.3.2. MedDRA

Following ICH M1 document, MedDRA dictionary will be used, in its last version. Fields should include MedDRA code. Any XML message containing MedDRA term description will be rejected.

2.3.3. Publications ICSR

For ICSRs originated from a publication, altogether with the expedited communication (online or XML transmission), a separate email containing the original paper (as attachment in a PDF file) will be sent to the following e-mail address fvicsr@agemed.es

The PDF file name will be the "worldwide unique case identification number" (A.1.10). And e-mail "subject" will contain the following text:

PUBLICATION (Reporter's (or First author) Autonomous Community) (Notification Number - A.1.0.1.)).

Some examples can be found below.

Example No 1

Company-1 wishes to report a publication depicting a case in Andalucía. Company-1 assigns a company notification number as: ES-Company1-45613231 and report it to the AEMPS.

The e-mail subject and the PDF file containing attached the publication will be as follows:

Subject (e-mail): **PUBLICATION (Andalucía) (ES-COMPANY1-45613231)**

PDF file Name (attached to email): **ES-COMPANY1-45613231.pdf**

Example No 2

Company-2 identifies a case occurring in Aragón that has been published. Company-2 assigns company notification number as: "ES-Company2-4321". Company-2 will send report to Company-1 and Company-1 will send report to the AEMPS with company notification number as: "ES-Company1-9876".

The e-mail subject and the PDF file containing attached the publication will be as follows:

Subject (e-mail): **PUBLICATION (Aragón) (ES-COMPANY1-9876)**

PDF file Name (attached to email): **ES-COMPANY2-4321.pdf**

It is highly recommended to use abbreviations title of scientific/medical publications and follow Vancouver's Uniform Requirements where coding the relevant field.

3. FURTHER CLARIFICATION

For any doubt, query or clarification please contact us by e-mail:

fvicsr@agemed.es

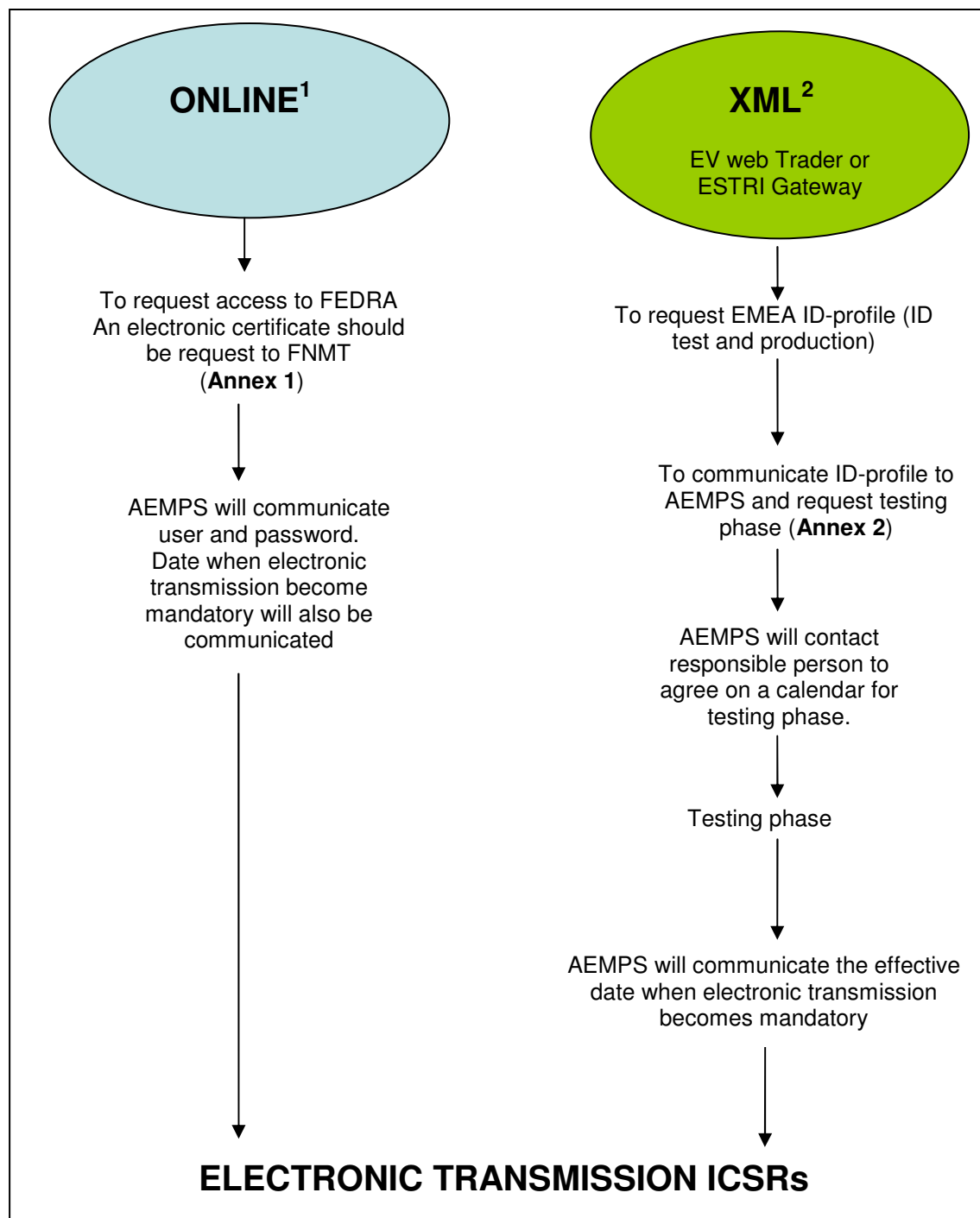
4. MORE INFORMATION (WEB PAGES)

- EMEA (European Medicines Agency)
<http://emea.europa.eu>
- EudraVigilance
<http://eudravigilance.emea.europa.eu>
- European Commission (Legislation)
http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
- European Commission – Volume 9A Human Pharmacovigilance
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf
- FNMT (Spanish authority to issue digital certificates)
<http://www.fnmt.es>
- Heads of Medicines Agencies (European Union)
<http://www.hma.eu>
- ICH (International Conference on Harmonisation), documents E2A, E2B(M), M1, M2
<http://www.ich.org/cache/compo/276-254-1.html>
- INE (to obtain Spanish cities INE codes)
<http://www.ine.es>
- MedDRA MSSO (Maintenance and Support Services Organization)
<http://meddramsso.org>
- Spanish Medicines and Healthcare products Agency (AEMPS)
<http://www.agemed.es>

5. ABBREVIATIONS LIST

AEMPS	<i>Agencia Española de Medicamentos y Productos Sanitarios</i>
CA	Competent Authority
CAFV	Pharmacovigilance Regional Centre
EMA	European Medicines Agency
ESTRI	Electronic Standards for the Transfer of Regulatory Information
EV	EudraVigilance
EV-PM	EudraVigilance-Post-Authorisation Module
EV-Web	EudraVigilance-Web
E2B	ICH document: data elements for transmission of ICSRs
FEDRA	Farmacovigilancia Española Datos Reacciones Adversas
FNMT	Fábrica Nacional de Moneda y Timbre
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities Terminology
M1	ICH document: medical terminology
M2	ICH document: electronic standards for the transfer of regulatory information (DTD, ESTRI)

5. DIAGRAM TO REQUEST ELECTRONIC TRANSMISSION



¹ Recommended for companies with a low volume of ICSR_s

² Recommended for companies with marketed products outside EEA



ANNEX 1

SOLICITUD DE CLAVE DE USUARIO PARA CARGA ONLINE EN FEDRA

Por la presente les informo que D/D^a _____

En calidad de _____

Del/de los Laboratorio/s (*)

(*) En caso de formar un **grupo de laboratorios** que compartan el Responsable de Farmacovigilancia y centralicen el intercambio de casos expeditivos de sospechas de RAM, incluir en la tabla el nombre de los laboratorios que forman parte del grupo. Se otorgará una única clave de usuario para todos los laboratorios. Si se quiere un usuario por cada laboratorio, en tal caso hay que enviar un formulario por cada laboratorio.

Solicita que la Agencia Española de Medicamentos y Productos Sanitarios **autorice el acceso** al sistema de información **SINAEM-FEDRA** a las siguientes personas como usuarios de FEDRA, con perfil '**Industria farmacéutica carga online**':

Nombre	1º Apellido	2º Apellido	E-Mail	DNI

Asimismo le informo que deben proceder a **dar de baja** como representantes de nuestra empresa a las siguientes personas:

Nombre	1º Apellido	2º Apellido	E-Mail	DNI

Finalmente le informo que la persona y dirección a la que deberán remitir **los casos expeditivos desde la AEMPS** son:

Nombre del Responsable FV en España	Dirección postal	Teléfono	Fax	E-mail

En _____, a ___ de _____ de 200_

Fdo. _____

PARA REMITIR A LA DIVISIÓN DE FARMACOEPIDEMIOLOGÍA Y FARMACOVIGILANCIA DE LA AEMPS

Dirigirlo al Registro General de la Agencia Española de Medicamentos y Productos Sanitarios en la C/ Campezo nº 1, CP 28022 de Madrid. La solicitud también puede realizarse enviando este formulario al número de fax 91 822 53 36 de la Secretaría de la División de Farmacoepidemiología y Farmacovigilancia o a la dirección de correo electrónico fvicsr@aged.es.



ANNEX 2

SOLICITUD DE PRUEBAS DE TRANSMISIÓN EN XML CON LA AEMPS

Por la presente le informo que D/D^a _____

En calidad de _____

Del/ de los Laboratorio/s (*)

(*) En caso de formar un **grupo de laboratorios** que compartan el Responsable de Farmacovigilancia y centralicen el intercambio de los ICSR con un único ID-Profile, incluir en esta tabla el nombre de los laboratorios que forman parte del grupo, tal como estén inscritas en el registro de Instalaciones farmacéuticas.

Solicita a la Agencia Española de Medicamentos y Productos Sanitarios **poder realizar las pruebas de transmisión en XML**. La persona encargada de la realización de las pruebas es:

Nombre del Responsable FV en España	Dirección postal	Teléfono	Fax	E-mail

Si otra persona diferente se encargará de las pruebas de transmisión, indicar:

Nombre del encargado de las pruebas	Dirección postal	Teléfono	Fax	E-mail

Los identificadores otorgados por la EMEA para la transmisión electrónica son:

ID-test (pruebas)	ID-producción

Modalidad:

- Envío y recepción de ICSR vía XML
- Envío de ICSR a AEMPS vía XML y recepción de ICSR de AEMPS en papel.

En _____, a ___ de _____ de 200_

Fdo. _____

La AEMPS (División Farmacoepidemiología y Farmacovigilancia) se pondrá en contacto con la persona encargada de la realización de las pruebas para indicarle las fechas y la forma en la que se realizará las pruebas de transmisión.

Dirigirlo al Registro General de la Agencia Española de Medicamentos y Productos Sanitarios en la C/ Campezo Nº 1, CP 28022 de Madrid. La solicitud también puede realizarse enviando este formulario al número de fax 91 822 53 36 de la Secretaría de la División de Farmacoepidemiología y Farmacovigilancia o a la dirección de correo electrónico: fvicsr@agemed.es