Pharmacovigilance information for pharmaceutical companies

Electronic exchanges of individual case safety reports (ICSRs) with ANSM
(National Agency of Medicine and Health Product safety)

This document supersedes the one published in October 2008 and updated in June 2009.

Last update: May 2012
A French version of this document is available.

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INTRODUCTION

This document:

- concerns the electronic transmission of ICSRs possibly related to medicines and products as
  listed in article R. 5121-150 of the French Public Health Code and received by exploitant
  pharmaceutical companies [note 1]. These ICSRs can be spontaneous or solicited reports
  transmitted by healthcare professionals, patients or other reporters, or post authorisation study
  reports.
- does not concern the transmission of suspected, unexpected and serious adverse reactions
  (SUSARs) occurring in the context of interventional clinical trials [ref 1]

The update of this document takes into account:

- the entry into force of the texts pertaining to the reporting of cases by patients, or patient
  associations (13 June 2011) [ref 2]
- under the interim arrangements related to Regulation 1235/2010 [ref 3], Directive 2010/84/EU [ref
  4] and the publication of the Good Pharmacovigilance Practices (GVP) [ref 5]. These provisions
  are applied from 21 July 2012. The transposition in French law of Directive 2010/84/EU is
  currently under progress in France [ref 6].

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1 The term “exploitant” is used in this document instead of the term “exploitant pharmaceutical company”.
Under the terms of article R. 5124-2, activity of exploitation is performed either by Marketing Authorisation Holder (MAH)
appointed in article L. 5121-8, of the Temporary Authorisation for Use mentioned in article L. 5121-12 or of one of the
registrations mentioned in articles L. 5121-13 and L. 5121-14-L, for the account of this holder, by another company or
organisation, or by both, each in this case responsible for one or more categories of operations covered by the operation of
the drug or product.
In accordance with European regulations (Directive 2004/27/CE [ref 7]), all Marketing Authorisation holders (MAH), located within the European Economic Area, are responsible for implementing a system guaranteeing the electronic transmission to the Health Authorities of ICSRs occurring subsequently to the marketing authorisation.

In agreement with the EMA, the GVP interim arrangements have been fitted in order to match with the current electronic transmission practice recommended in France since 2008. The final arrangements shall apply once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation [ref 3] are established.

From 1 January 2013 on, the transmission of ICSRs must be done electronically. Non-electronic transmission (by fax or regular mail) will not be accepted.
A) TRANSMISSION of ICSRs OCCURRING IN FRANCE, WHATEVER THE REPORTER

- SERIOUS

<table>
<thead>
<tr>
<th>Marketing Authorisation Procedure</th>
<th>Occurrence country</th>
<th>Adverse reaction type (time frame)</th>
<th>Transmit to Interim arrangements (source: GVP)</th>
<th>Transmit to French Interim arrangements (starting 21 July 2012)</th>
<th>Transmit to Final arrangements (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centralised</td>
<td>France</td>
<td>Serious (15 days)</td>
<td>Member state where suspected adverse reaction occurred</td>
<td>Situation 1 : Eudravigilance database OR Situation 2 : French pharmacovigilance database (for MAHs already in production with the French pharmacovigilance database as of 21 July 2012) OR Situation 3 : Fax/ regular mail (allowed until 31 December 2012)</td>
<td>Eudravigilance database</td>
</tr>
<tr>
<td>Mutual recognition, decentralised, or subject to referral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purely national</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments on the French interim arrangements (starting 21 July 2012):

**Situation 1** (or awaiting situation 1) – (See appendix 1 for technical specifications)
- Transmission to **Eudravigilance currently in production** → transmission to be continued
- Transmission to **Eudravigilance currently in testing phase** → paper transmission (fax/regular mail) is accepted only until 31 December 2012 before going into production with Eudravigilance

**Situation 2**:
- **Electronic transmission to ANSM currently in production**
  → Either continuation of this transmission to ANSM: in this case, ANSM is in charge of the electronic re-transmission to Eudravigilance of any ICSRs occurring in France transmitted by the exploitants: hence, the exploitants must not submit the ICSRs directly to Eudravigilance in order to avoid duplicate cases in the European database.
  → Or switch to direct transmission to Eudravigilance (situation 1)

**Situation 3**:
- **Paper transmission (fax/regular mail) to ANSM currently established**
  → Switch to direct transmission to Eudravigilance as soon as possible (situation 1).
  Non-electronic transmission (fax/regular mail) shall not be used to send ICSRs to ANSM from 1 January 2013 on.

**Note**: Up to July 2012, non-medically confirmed serious ICSRs occurring in France, reported since 13 June 2011 should be transmitted as "backlog" cases, if not transmitted prospectively. The technical specifications for electronic transmission of ICSRs (in accordance with the EMA) are described in appendix 1.
**B) TRANSMISSION of ICSRs OCCURRING OUT OF FRANCE, WHATEVER THE REPORTER**

**a) ICSRs OCCURRING IN THE EUROPEAN UNION (outside France)**

- **SERIOUS AND NON-SERIOUS**

<table>
<thead>
<tr>
<th>Marketing Authorisation Procedure</th>
<th>Occurrence country</th>
<th>Adverse reaction type (time frame)</th>
<th>Transmit to Interim arrangements (source: GVP)</th>
<th>Transmit to French Interim arrangements (starting 21 July 2012)</th>
<th>Transmit to Final arrangements (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centralised</td>
<td>France</td>
<td>Non serious (90 days)</td>
<td>Member state where suspected adverse reaction occurred, if required</td>
<td>Not required by France</td>
<td>Eudravigilance</td>
</tr>
<tr>
<td>Mutual recognition, decentralised, or subject to referral</td>
<td>European Union (outside France)</td>
<td>Serious (15 days) and Non Serious (90 days)</td>
<td>Member state where suspected adverse reaction occurred (serious)*</td>
<td>See transmission procedures applicable in each EU member state.</td>
<td>Eudravigilance</td>
</tr>
</tbody>
</table>

*N Note: Up to July 2012, if non-medically confirmed serious ICSRs occurring in the EU (outside France) are not available in EudraVigilance (due to EU member states local regulations), and if France is rapporteur or reference member state, such ICSRs are to be transmitted to ANSM via physical media (CD-ROM).*
b) ICSRs OCCURRING OUTSIDE THE EUROPEAN UNION

<table>
<thead>
<tr>
<th>Marketing Authorisation Procedure</th>
<th>Occurrence country</th>
<th>Adverse reaction type (time frame)</th>
<th>Transmit to Interim arrangements (source: GVP)</th>
<th>Transmit to French Interim arrangements (starting 21 July 2012)</th>
<th>Transmit to Final arrangements (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Centralised</td>
<td>Non-EU</td>
<td>Serious (15 days)</td>
<td>• Eudravigilance database</td>
<td>Eudravigilance</td>
<td>Eudravigilance</td>
</tr>
<tr>
<td>• Mutual recognition, decentralised, or subject to referral</td>
<td></td>
<td></td>
<td>• Member states where medicinal product is authorised, if required</td>
<td>Not required by France. ICSRs are available in Eudravigilance</td>
<td></td>
</tr>
<tr>
<td>• Purely national</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Up to July 2012, non-medically confirmed serious ICSRs occurring outside the European Union, and reported since 13 June 2011 should be transmitted to Eudravigilance as "backlog" cases, if not transmitted prospectively. The technical specifications for ICSRs electronic transmission (in accordance with the EMA) are described in appendix 1.

**NOTES**

* Serious ICSRs reported to ANSM via the network of the French Regional Pharmacovigilance Centres are transmitted by ANSM to EMA (via Eudravigilance) since 20 November 2005. These ICSRs are also transmitted, by regular mail, and for their information, to the exploitants of the drugs identified as suspect or interacting in these ICSRs.

This system has not been modified and also applies to serious ICSRs reported by patients or patient associations or any other reporter (whether these reports are medically confirmed or not).

It should be noted that, in order to avoid duplicates, these ICSRs must not be retransmitted by the exploitant to Eudravigilance.

* When submitting electronically to ANSM scientific and medical literature ICSRs, a full copy of the article should also be sent to ANSM, either by fax or by regular mail, stating the company name, address, phone number, email address and references to the Worldwide unique case identification number and to the related medicinal product (see address and fax number below in paragraph C).

* The transmission dispositions according to a national pharmacovigilance monitoring programme or a national compassionate use programme remain unchanged and still require transmission as defined above in this document.
C) PROCEDURES FOR EXCHANGE WITH THE PHARMACOVIGILANCE DEPARTMENT

Companies not having notified ANSM, since June 2009, of their ICSR transmission dispositions, or if modifications have been made to these dispositions since their last notification to ANSM, are required to do so by regular mail, specifying:

- the subject heading: "Electronic transmission of ICSRs".
- the date of effective or scheduled electronic transmission of ICSRs to EudraVigilance
- the company's interchange ID

to the following address:

Dr Evelyne Falip
ANSM
Pharmacovigilance Department
143/147 boulevard Anatole France
F-93285 Saint-Denis Cedex.
Fax: 00 33 (0)1 55 87 35 32

For information, please send an e-mail to: pharmacovigilance@ansm.sante.fr.
Please do not send any ICSRs to the above email address.

D) REFERENCES

1) Avis aux promoteurs d'essais cliniques de médicaments : mise en place et conduite en France d'essais cliniques portant sur des médicaments à usage humain
http://www.ansm.sante.fr/var/ansm_site/storage/original/application/9887ae44251182f7e7dd9cda854b1b4.pdf


6) Transposition Decree to be published.

APPENDIX 1

TECHNICAL SPECIFICATIONS FOR THE TRANSMISSION OF ICSRs TO EUDRAVIGILANCE

The EudraVigilance Post-Authorisation Module (EVPM) is designed for post-authorisation ICSRs. Accordingly, the receiver's ID of the ICSRs must be: EVHUMAN. The procedure for the initiation of the electronic transmission of ICSRs to EudraVigilance is described on the EV website: http://eudravigilance.ema.europa.eu/human/TenSteps.asp The validation rules (business rules) are those used by the EudraVigilance system (Doc. Ref. EMEA/H/20665/04/Final).

MedDRA

The MedDRA terms used must belong to the latest published version of this terminology. The lowest level terms (LLTs) must also be “current” in this latest published version. The notion of latest published version must conform to the recommendations of the MSSO (MedDRA Maintenance and Support Services Organization) and the EMA's EudraVigilance Expert Working Group.

Languages

Languages accepted by ANSM in the framework of electronic transmission of ICSRs are French and English.

Imputability

For cases occurring in France: the drug causality assessment according to the French method of imputability must be included in the ICSRs in section B.4.k.18 (Relatedness of drug to reaction(s)/event(s)) of the E2B message. The method used (B.4.k.18.3) must be labelled “FRENCH IMPUTABILITY METHOD” and the result (B.4.k.18.4) indicated in “CxSyBz” format (where x, y and z represent the chronological, semiological and bibliographic imputability scores respectively).

Patient/consumer/non-healthcare professionals ICSRs

Technical details for submitting to EudraVigilance non-medically confirmed serious cases occurring in France or out of the European Union: (ref 2):

- For serious patient/consumer cases which are to be sent prospectively, the ICH M2 data element M.1.1 'Message type' should be populated with the value "ichicsr". Please note that this field is case sensitive and should be populated in lower case.

- For serious patient/consumer cases which are to be sent retrospectively from 13 June 2011, the ICH M2 data element M.1.1 'Message type' should be populated with the value "backlog". Please note that this field is case sensitive and should be populated in lower case.

- The retrospective ICSRs can be submitted using physical media in line with the applicable ESTRI recommendations (CD, DVD). The acknowledgments for these cases will be returned via the gateway.

- The MAH should not resend periodic ICSRs for those cases that have already been sent prospectively or retrospectively in line with the above.

- Serious consumer cases occurring in EEA Member States other than France, which are related to a medicinal product for which France is the RMS or Rapporteur, should not be sent to EudraVigilance.
APPENDIX 2

CONSEQUENCES ON E2B TRANSMISSION OF THE RENAMING OF THE FRENCH AGENCY
(AFSSAPS BECOMING ANSM)

1. Only for companies already transmitting directly ICSRs to ANSM

Section RECEIVER (A.3.2) of E2B messages should ideally be populated as follows. Section A.3.2 is not parsed or further analysed upon reception at ANSM, so no ICSR will be rejected for not following this recommendation.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.3.2.1</td>
<td>ReceiverType</td>
<td>2</td>
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</tr>
<tr>
<td>A.3.2.2a</td>
<td>ReceiverOrganization</td>
<td>ANSM</td>
<td></td>
</tr>
<tr>
<td>A.3.2.2b</td>
<td>ReceiverDepartment</td>
<td>Département de Pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td>A.3.2.2c</td>
<td>ReceiverTitle</td>
<td>Dr</td>
<td></td>
</tr>
<tr>
<td>A.3.2.2d</td>
<td>ReceiverGiveName</td>
<td>Pascal</td>
<td></td>
</tr>
<tr>
<td>A.3.2.2f</td>
<td>ReceiverFamilyName</td>
<td>AURICHE</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3a</td>
<td>ReceiverStreetAddress</td>
<td>143/147, Bd Anatole France</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3b</td>
<td>ReceiverCity</td>
<td>SAINT-DENIS</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3d</td>
<td>ReceiverPostCode</td>
<td>93200</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3e</td>
<td>ReceiverCountryCode</td>
<td>FR</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3f</td>
<td>ReceiverTel</td>
<td>155873560</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3h</td>
<td>ReceiverTelCountryCode</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3i</td>
<td>ReceiverFax</td>
<td>155873532</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3k</td>
<td>ReceiverFaxCountryCode</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>A.3.2.3l</td>
<td>ReceiverEmailAddress</td>
<td><a href="mailto:pharmacovigilance@ansm.sante.fr">pharmacovigilance@ansm.sante.fr</a></td>
<td></td>
</tr>
</tbody>
</table>

2. For all companies

In order to maintain consistency among all pharmacovigilance databases, and until further notice:

2.1 Section REPORTDUPLICATE (A.1.11) of E2B messages must be populated as follows.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1.11.1</td>
<td>DuplicateSource</td>
<td>ANSM</td>
<td></td>
</tr>
<tr>
<td>A.1.11.2</td>
<td>DuplicateNumb</td>
<td>Keep Number FR-AFSSAPS-xxxxxx</td>
<td></td>
</tr>
</tbody>
</table>

2.2 Section LINKEDREPORT (A.1.12) of E2B messages must be populated as follows.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1.12</td>
<td>LinkReportNumb</td>
<td>Keep number FR-AFSSAPS-xxxxxx</td>
</tr>
</tbody>
</table>