Part III. Q&A related to the official Eudravigilance communication

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Subject: Reporting

1. Is circular 460 still relevant for reporting to the FAMHP? Or does the communication need to be followed?
There is a contradiction with circular 460 concerning the reporting of SUSARs and NON-SUSARS (SESARS). We would like to have some explanation.

It has been planned for a while to rewrite circular 460, that is still mainly addressed to partners who don't report electronically, in consultation with the R&D division of the FAMHP. An update should be made as a result of the "mammoth legislation" (R.D. dd. 14 DECEMBER 2006. — Royal decree concerning medicinal products for human and veterinary use) and of the modification of the CT3-guideline. The latter will be awaited before launching the new circular replacing circular 460. The new circular will also describe the reporting modifications, related to the new procedures.
The new Volume 9A clearly states that:
"Interventional studies fall under the provisions of Directive 2001/20/EC on clinical trials and adverse reactions should be reported in line with that Directive and associated guidance, in particular the Detailed Guidance on the collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (ENTR/CT3, vol. 10 of the Rules Governing Medicinal Products in the EU, Chapter II)."
This is in contradiction to the former Vol. 9 that was applicable at the moment when circular 460 was written, namely:
The marketing authorisation holder should report, on an expedited basis, all serious suspected adverse reactions, occurring within the European Union and brought to its attention by a health-care professional to the competent authority in the member state in whose territory the incident occurred.
In the old Vol. 9, no distinction was made between reports from clinical trials and other reports (spontaneous, non-interventional studies, …).

REMARK : According to the RD of 14/12/2006 the Vol. 9 must be applied in its most recent form, which is Vol. 9A:

Art. 199. The collection, the verification, the presentation and the periodicity of the reports over adverse reactions, as well as the electronic exchange of information concerning pharmacovigilance happens according to the detailed guidelines issued by the European Commission in the "Guidelines on Pharmacovigilance for Medicinal Products for Human Use in the European Union", as they appear in the last available version as well as according to Annex III of this decree.

CONCLUSION:
Reporting of SESARs (Suspected Expected Serious Adverse Reactions) from interventional clinical trials by MAHs does not longer apply. A renewed circular will be written after the definitive publication of CT3.
Please be informed that expedited reporting rules to Ethic Committees, as discussed in circular 460 are still applicable, whether the partner is reporting electronically or not.

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2. Does a MAH need to send reports from interventional clinical trials (for which the MAH is not the sponsor)?

Reporting of SUSARs from interventional clinical trials by MAHs that are not sponsor of the study is no longer possible.
This results from the new business rules which are currently applied since their implementation in the European Eudravigilance system on the 7th of February 2011. For each report from an interventional clinical trial, a EudraCTnumber should be included. If you do not have this number, you are not able to send the message to Eudravigilance and it is not your responsibility. Therefore, SUSARs can only be reported by the sponsor of the clinical trial.

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3. At company X, cases from interventional clinical trials are already submitted to EVCTMPROD by our headquarter. The workflow for other serious ICSR (labelled + unlabelled) can easily be switched at headquarter level from the local Belgian organisation to EVHUMAN. Since local screening of cases will be bypassed, this may however result in over-reporting. Will the FAMHP agree with this ?

The FAMHP is aware that "over-reporting" can occur as a result of the fact that the headquarter is performing the electronic reporting, that in case of company X will decide what must be sent to the FAMHP. Nevertheless, this

remains an internal arrangement within the company. MAH and sponsors need to take the necessary internal measures in order to avoid over-reporting.
As MAH, for the reports in the context of the "vigilance" (as mentioned in the official communication) legislation, the FAMHP doesn't expect any problem : all ADRs occurred in Belgium (expected as well as unexpected) should be reported.

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4. Some points in the official communication are not clear to us at all. If we have properly understood the content of this letter, each company must as from 1 June 2011 directly report adverse reactions in the Eudravigilance system.

Indeed, this is what is mentioned in the communication. Nevertheless, some transition measures are proposed, see <u>Part II. Technical requirements.</u>

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5. On 24th of December 2010, we received a message from the FAMHP concerning the problems of the local Eudravigilance programme and also the information that no new partners could be admitted to this programme.

As a result of the local problems since March 2010, internal adaptations had to be made in order to be able to receive and process the reports from partners who were already reporting electronically, namely the receipt of reports as webtrader (for more information, see Part I. Historical overview) within the European Eudravigilance system.
These adaptations required and still require the involvement of extra resources from the FAMHP in order to be able to continue processing these reports and guaranteeing the reporting to the EMA.
This implies:

- **Extended process of transmission of the reports to the EMA because the distinction between the CT and PM module has to be done manually (in the former local Eudravigilance system, this distinction was done automatically, it was only necessary to decide which report had to be sent);**
- **Manual creation of acknowledgements (previously, this was done fully automatically from the local Eudravigilance system); this process needs to be executed within 2 working days.**

This internal procedure was new for the FAMHP and had to be started up urgently as the EMA had sent 900 blocked messages to the FAMHP on the 16th of April 2010. Since then, this new internal procedure has been applied.
For these reasons, at that time, the FAMHP could not accept new partners for the electronic reporting.
This internal procedure still applies today but has been simplified.
As a result of the adaptation to the reporting process as proposed in the communication, the procedure described above will be stopped in the future.
Every new partner who registers for electronic reporting to the FAMHP, must already be registered in the production environment of the Eudravigilance system of the EMA. For this, they had to carry out the required testing procedures in the testing environment within the Eudravigilance system of the EMA, for the reports that must be sent to the PM-module, including the spontaneous reports and the reports from non-interventional studies and others (e.g. registries, compassionate use) as well as for the reports from clinical trials that must be sent to the CT-module. Afterwards, they are again closely followed up during a certain period in the production system of the EMA.
This means that each partner who already reports electronically has the capability to send all reports according to the procedure as asked for in the communication.

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6. Several companies are actually not ready for electronic reporting to Eudravigilance because the necessary internal IT developments are still ongoing and no trainings have already taken place to be able to comply. What do they need to do?

Before a partner can do the testing procedure for the electronic reporting with the EMA, the organisation has to send a person to the Eudravigilance User Training course; this person must have succeeded the exams linked to the course. It is not necessary that everybody within the same organisation follows the training; the person who has followed the training must pass the information internally to his/her colleagues.
Furthermore, there is no obligation for the QPPV to follow this training or to carry out the necessary reporting tasks practically.
For further information : see <u>Part II. Technical Requirements</u>.
Remark : Partners who are not ready to report electronically to EMA's Eudravigilance, are also not ready to report electronically to the FAMHP.

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7. A lot of companies have concluded from this note that just a change of e-mail address has taken place!

It does not concern the simple change of an e-mail address but the change of the receiverID within the "Eudravigilance community" to which the ADRs must be reported.
Nevertheless, all reportable information, not available in the E2B-format, and any additional information concerning CIOMS (e.g. literature articles…) should be sent to the FAMHP, preferably by e-mail. From now on, all communication about CIOMS is managed through one common e-mail address for the R&D division (under the Directorate General Pre) and the Vigilance division (under the Directorate General Post), which is icsr@fagg-afmps.be.

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8. Can we understand from the note that the local reporting to the FAMHP is fully replaced by reporting to the 2 concerned European databases? We would like to know about the effects of the procedure to be followed (with reference to circular 460 and communication 24/12/2010).

There are no 2 European databases, but two modules within the European Eudravigilance system, which are the CT- and the PM-module.
This implies that a report from a clinical trial follows another way to the European database than a spontaneous report and a report from a non-interventional clinical study and others (e.g. registries, compassionate use) (See scenario C in Part I. Historical overview). This is necessary to define the access modalities of sponsors of clinical trials and MAHs, and probably also an easy way to be able to select the right business rules set (spontaneous or clinical trial) at the moment of the sending of data to the European Eudravigilance-database.
Whatever to which module the report is sent, all reports arrive in the same database, Eudravigilance. The module determines the access rights to this report in the European system. Sponsors of clinical trials who have sent their reports to the CT-module do not have access to their reports in the European Eudravigilance system. MAH who have sent their reports to the PM-module, have access to the reports that they have sent themselves to the European Eudravigilance system.
The rule concerning which module must be used for the sending is very simple:

The SUSARs from interventional clinical trials* must be sent to the EVCTMPROD module. **The other reports* must be sent to the EVHUMAN module.**

*** which need to be sent according to the applicable national and European legal framework, mentioned in the official Communication**

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9. Will there be a notification coming from the EU database to the FAMHP or will the Agency collect itself the info in the EU database?

As a result of the new business rules that have come into effect on the 7th of February 2011 in the European Eudravigilance system the population of the "Primary source country" field with "Belgium" has become an obligation. Nowadays, the FAMHP is able to collect the Belgian reports. The FAMHP will continue performing its vigilance tasks for which it has the obligation. The so-called "rerouting" system is not yet developed in the context of the new vigilance legislation. Whether the FAMHP will use it in the future, will be decided at a later stage.

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10. What about the reporting of adverse reactions from studies that have no EUDRACTnumber?

The Eudract-number is only mandatory for interventional clinical trials for which there is a reporting obligation.
The new business rules provide for the following regulation concerning Eudract-numbers*:

- *a./ The following generic EudraCT Number is provided for all interventional clinical trials including a centre in a Member State and started before 01 May 2004 (or before the clinical trial Directive 2001/20/EC has been implemented in a Member State): EVCT-000000-16. It should be used in the data element studyname (ICH E2B(R2) A.2.3.1 for these interventional clinical trials only. It should be followed by the '#' symbol and the study abbreviated name.**
- *b./ ICSRs originating from interventional clinical trials, which need to be reported by MAHs to EVCTM in accordance with the requirements described in Volume 9A of the Rules Governing Medicinal Products in the European Union, should include the following generic EudraCT number EVCT-999999-25, followed by the '#' symbol and the study abbreviated name. This is to be able to exclude these ICSRs from the 7 days expedited reporting compliance monitoring. It should be used in the data element studyname (ICH E2B(R2) A.2.3.1 for*

*cases which occurred outside the EEA in interventional clinical trials for which the opdrachtgever has NO reporting obligation of these cases in the EEA under the Directive 2001/20/EC.**

(*ref : Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) : EMA/H/20665/04/Final Rev. 2 dd. 15/10/2010)

Based on point a./ for reports interventional clinical trials, authorized or started before the implementation of the Directive 2001/20/EC within the national legislation, the "Eudractnumber" field should be populated with "EVCT-000000-16".

Based on point b./ for reports fro; interventional clinical trials that have occured outside Europe, they can use EVCT-999999-25 as data for the "Eudract number" field.

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11. How will this be communicated to companies that carry out clinical trials as a sponsor but are not MAH yet ? They don't receive these circulars. That's why there is an absolute necessity to make the new procedure available in English on the website of the FAMHP.

The official communication will be published on the website of the FAMHP and will also be available in English.
The R&D division will also do the necessary to distribute this document to the sponsors of clinical trials.

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12. Will the FAMHP provide trainings to report electronically in Eudravigilance?

The EMA has already officially asked the question whether Member States can offer the possibility to organize trainings elsewhere than in London. It will be further examined if the FAMHP has the possibility to organise it.

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13. Following the mentioned legislation references in the official communication, our reporting obligations are different from those mentioned in Circular 460 :
The Circular states that MAHs and sponsors that report electronically have an exemption for the "non-Belgian" reports. Does it mean that we need to report more then previously?

The official communication is a formal document in which the legal reporting obligations for partners, related to the reporting of ADRs are listed.
Nowadays because of the legal changes that became applicable after Circular 460, other obligations also came into application. e.g. reporting obligations as reference memberstate.
A MAH fullfils all his expedited reporting obligations to the FAMHP, if he complies to Vol. 9A, including the reporting requirements to the European Eudravigilance database and to other Member States.
Sponsors fullifil their obligation as they need to send their reports to the European Eudravigilance database.

Subject: Technical aspects

1. We are very surprised about the unexpected communication of the change of reporting system. You can most probably imagine that such changes require an important adaptation of the existing reporting procedures within the companies, not only in Belgium but also at head quarters' level. Moreover, the indicated deadlines are extremely short and not realistic in terms of realisation. Even the transition period seems much too short to us to organize this.

This new reporting system has already been discussed for some months. Our communication of 24 December 2010 stated the following:
"In the context of the total migration project of the ICT-infrastructure within the FAMHP, the "Eudravigilance" project to resolve the problems with our local Eudravigilance programme is currently under discussion. You will be informed as soon as possible of the new process for electronic reporting."
The modifications that are asked for are technically speaking not insuperable according to the FAMHP. First and foremost, each partner already needs to be able to send to the Eudravigilance system of the EMA (to the PM-and/or to the CT-module) (depending on the status in the electronic community: as MAH or as sponsor of clinical trials).
A. Reports from clinical trials that previously had to be reported to the FAMHP with "AFIGP" as receiverID, must also fully comply with the business rules of a clinical trial in general and as these are implemented in the EMA system
(LINK : http://eudravigilance.ema.europa.eu/human/docs/guid¯P¯Technical%20Documentation¯EMEA-H-20665-04-en-Final_Revision_2.pdf).
Sponsors already had the obligation to send all these reports to the CT module of the European Eudravigilance database, using the EVCTMPROD as receiverID.
Sending to the FAMHP according to the new procedure is thus no longer required.
B. Spontaneous reports and reports from non-interventional studies and others (e.g. registries, compassionate use) that previously had to be sent to the FAMHP with "AFIGP" as receiverID, must also fully comply with the business rules of a spontaneous reporting in general and as these are implemented in the EMA system (LINK : http://eudravigilance.ema.europa.eu/human/docs/guid¯P¯Technical%20Documentation¯EMEA-H-20665-04-en-Final_Revision_2.pdf).
Only at the level of the XML-file, the receiverID must be adapted according to the new procedure, namely:
from receiverID "AFIGP" to "EVHUMAN" (which corresponds to the PM-module of the European Eudravigilance database).
To this end, adaptations are only necessary at the level of the XML header:
You can find more information in the introduction, Part II "Technical adaptations"or requirements ?.
It's important that the headquarters that are practically involved in the electronic sending process, are directly informed .
To this end, an English version is also available on the website.
Furthermore, the FAMHP wants to remark the following:
a./ It is not the intention to stop the receiverID "AFIGP" of the FAMHP as of 1st June 2011. The current way of reporting will continue to exist but the FAMHP requests for an engagement : partners who are not ready to report following the new procedure should inform the FAMHP by sending their implementation plan with timetable to the FAMHP by the 1st of June 2011 to icsr@fagg-afmps.be.
b./ The FAMHP has already discussed with some MAHs and sponsors of clinical studies concerning this new procedure that in fact simplifies the way of reporting. The FAMHP hasn't heard any negative reactions about this yet.
c./ Sweden has actually already introduced this way of reporting. The Netherlands will follow by the end of this year. They have already introduced this rule for the CT reports several years ago.

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2. Furthermore, it's important that the official communication will also be available in English and that a specific contact person who is available for answering potential (technical) questions (by e-mail or phone) will be designated during the transition period.

The "official communication" will also be provided in English and will be available on the English part of the website of the FAMHP. The e-mail address icsr@fagg-afmps.be, as indicated in the communication, is the contact address for further questions. If a contact by phone is required, this can happen by appointment via the same e-mail address.
In case of technical problems, please contact the EMA (see Part II. Technical requirements).

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3. Continuity plan: If there is a problem with the transmission of adverse reactions to the database of the EMA, these are sent in that case to the EMA in paper format. Do these have to be sent in that case at the same time to the FAMHP?

Since the FAMHP must continue to execute its vigilance tasks despite the modification of reception of the reports, the FAMHP must also be informed of these reports in case of problems in Eudravigilance; this also applies to reports from literature articles for which the FAMHP has the obligation to transmit the article to the EMA.
With this communication, the FAMHP wants to seize the opportunity to launch one common entry point for information related to expedited reporting, namely the e-mailaddress icsr@fagg-afmps.be to which both the "R&D" and the "Vigilance" division have access.

Subject: New partners

Among those members who still don't report electronically, there is a huge confusion and frustration concerning the timing for admission in the testing programme for Eudravigilance. Is there now already more clearness about this?

Since they have already tested with the EMA and since the new business rules already handle the reporting more strictly, new partners do not need to pass trough a "local" testing procedure.

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2. Besides, we wonder if the company will be obliged as from the 1th of June to report an adverse reaction via this system. I assume that it will not be the case since there are still companies in the queue for the local testing of their reporting system.

The FAMHP requests for an engagement : partners who are not ready to report following the new procedure should inform the FAMHP by sending their implementation plan with timetable to the FAMHP by the 1st of June 2011 to icsr@fagg-afmps.be.
The local testing process will be entirely abandoned since no testing environment with received ID "TAFIGP" in the local (Belgian) Eudravigilance system is available. The partners who were queuing for the electronic reporting to the FAMHP can immediately follow the new procedure. As a result of the new business rules introduced on 7 February 2011, there is already an extra control on the content of the reports.
In the context of the new legislation, punctual controls will be carried out. If the FAMHP is faced with problems with this, it will inform the vigilance inspectors. Furthermore, the EMA has also started up a project since December 2010 to review the quality of reports, already available in the European Eudravigilance database and future ones.

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3. It's appropriate that the circular states something concerning the two items mentioned above (see question I & II).

The communication will be released in its current form since this complies with the current legislation.
This Q&A document gives an explanation for the "official communication".

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4. MAHs have been requested some time ago to register for electronic reporting to the FAMHP but further actions were then not mentioned, that's why this measure appears as a complete surprise.

The objective was to personally inform these parties of the communication.
The partners (MAHs and Sponsors) who have registered themselves to the EMA as a result of this question and who have passed the testing procedures with the EMA, can go in production, i.e. send the Belgian reports to the EMA without any testing with the FAMHP.
When new partners have installed the procedure for "direct" electronic transmission to the FAMHP, using the receiverID "AFIGP", they can face problems to re-adapt their system for transmission to the EMA's modules in a short term. Therefore, the FAMHP has the following proposal: They can go immediately into production by reporting to the receiverID "AFIGP" under one condition, namely that their system is fully compliant with the new business rules of the 7th of February 2011. Nevertheless, the FAMHP requests for an engagement : partners who are not ready to report following the new procedure should inform the FAMHP by sending their implementation plan with timetable to the FAMHP by the 1st of June 2011 to icsr@fagg-afmps.be.
If the FAMHP observes the need to create a high number of negative messages when creating report acknowledgements to the partner, this would be for the FAMHP a sound reason to refuse the partner to continue electronic reporting to the FAMHP (on the AFIGP address).

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5. Does this communication replace the one of 24/12/2010? If so, does it mean that the FAMHP is ready to accept new candidates in the electronic reporting programme?

This communication is rather a supplement. This is also addressed to the new candidates who can follow this new procedure if they are ready for it and as indicated in the previous question, they can also send temporarily to AFIGP.

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6. What about the (small) companies that still do not report electronically for the moment?

MAHs who don't report electronically yet and haven't registered themselves as a candidate to the FAMHP must submit an implementation plan with timetable to the FAMHP by the 1st of June 2011. They must set themselves in order with the current national and European legislation. The European Eudravigilance system is a useful tool, also for small enterprises.

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7. Since there is no more reporting to the FAMHP, we wonder if the service that the FAMHP offered to small companies will continue to exist and if not, how can this be handled?
The same applies to academic centres that carry out studies and that cannot register as such to Eudravigilance. Is there a distinct process provided for them?

As long as a partner doesn't have the possibility to report electronically, the FAMHP will take its responsibility and send to the EMA the reports in the European Eudravigilance system, on the basis of the CIOMS reports that it can receive in a non E2B-format, preferably, by e-mail or others like fax and post. The partners are encouraged to comply as soon as possibe to the current legislation and the new procedure (implementation plan with timetable is requested for the 1st of June 2011). This applies for MAH as well as for commercial sponsors.
For non-commercial sponsors, the FAMHP has not yet taken a position.

For more information concerning electronic reporting:

- **Volume 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for medicinal products for human use (http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm**
- **Volume 10 Clinical trials guidelines (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm)**
- **See Q&A document Vol.9A : Eudravigilance expert working group volume 9a implementation - questions & answers - Version 3.2 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006318.pdf)**
- **See Q&A document Vol.10 : The rules Governing documents applying to clinical trials Volume 10 - questions & answers - Version 7.0 (http://ec.europa.eu/health/files/eudralex/vol-10/v10_chap5_qa_v7.pdf)**
- **New business rules dd. 07 February 2011 : Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) : EMA/H/20665/04/Final Rev. 2 dd. 15/10/2010 (https://eudravigilance.ema.europa.eu/human/docs/guid¯P¯Technical%20Documentation¯EMEA-H-20665-04-en-Final_Revision_2.pdf)**
- **Eudravigilance website : http://eudravigilance.ema.europa.eu**