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QUESTION AND ANSWERS

ON TRANSITIONAL ARRANGEMENTS CONCERNING THE ENTERING INTO FORCE OF THE NEW PHARMACOVIGILANCE RULES PROVIDED BY DIRECTIVE 2010/84/EU AMENDING DIRECTIVE 2001/83/EC AND REGULATION (EU) NO 1235/2010 AMENDING REGULATION (EC) NO 726/2004

The entering into force of the new pharmacovigilance rules raises legal and practical questions as regards the date from which the new rules apply. This Q&A document provides answers to some of those questions and may be complemented with further items if need be.

Interested stakeholders may also check the website of the European Medicines Agency (www.ema.europa.eu) or HMA (www.hma.eu) for further guidance on transitional matters.

1. RENEWAL APPLICATIONS

Question: The new pharmacovigilance legislation modifies the submission deadline for renewals from 6 months to 9 months as well as content requirements. From which date do the new requirements and deadlines for renewals apply?

As of 2 July 2012 submissions of renewal applications for centrally authorised products have to comply with the data requirements provided by Article 14(2) of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010. The 9-months deadline provided by the same Article should however apply only to products for which the marketing authorisation ceases after 2 April 2013. Likewise, submissions of renewal applications for nationally authorised products have to comply as of 21 July 2012 with the data requirements provided by Article 24(2) of Directive 2001/83/EC as amended by Directive 2010/84/EU. The 9-months deadline provided by the same Article should however apply only to products for which the marketing authorisation ceases after 21 April 2013.

2. MARKETING AUTHORISATION APPLICATIONS PENDING AT THE DATE WHEN THE NEW PROVISIONS START TO APPLY

Question: My marketing authorisation application has been submitted prior to the date of application of the new pharmacovigilance legislation (ie. 2 July 2012 for centralised procedure applications and 21 July 2012 for national applications), however, the procedure will only be finalised after that date. Do I have to "upgrade" my application in accordance with the new requirements?

No, applicants of a pending marketing authorisation application do not have to modify their application dossier when the new rules start to apply. However, upon their own initiative, applicants may contact the competent authorities if they wish to replace after July 2012 in their pending application the detailed description of the pharmacovigilance system by the new summary of the pharmacovigilance system (including the reference to the location of the pharmacovigilance system master file (PSMF)). Competent authorities may agree on such replacement on a case-by-case basis provided that the summary and the pharmacovigilance system master file fully comply with the new legal requirements.

The pharmacovigilance system master file will have to be in place either at the time of the date of renewal or by 2 July 2015 (Regulation) /21 July 2015 (Directive), whichever is the earliest.

3. PHARMACOVIGILANCE SYSTEM MASTER FILE

Question: Does the requirement for a pharmacovigilance system master file apply to all existing marketing authorisations, even if my initial application did not contain at the time of submission a detailed description of the pharmacovigilance system?

Yes, the obligation to maintain a pharmacovigilance system master file applies to all holders of marketing authorisations granted in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 regardless whether or not the marketing authorisation contains currently a detailed description of the pharmacovigilance system.

Question: My renewal application has been submitted prior to the date of application of the new pharmacovigilance legislation (ie. 2 July 2012 for centralised procedure applications and 21 July 2012 for national applications), however, the procedure will only be finalised after that date. Do I have to "upgrade" my application in accordance with the new requirements for the pharmacovigilance system master file?

No, applicants of a pending renewal application do not have to modify their application dossier after the new rules for the pharmacovigilance system master file start to apply. However, upon their own initiative, applicants for renewals may contact the competent authorities if they wish to supplement the pending renewal application with the information that they maintain a pharmacovigilance system master file. On a case-by-case basis competent authorities may accept to include this point in the renewal application provided that the summary and the pharmacovigilance system master file fully comply with the new legal requirements.

The pharmacovigilance system master file will have to be in place either at the time of the date of the following renewal, if applicable, or by 2 July 2015 (Regulation) /21 July 2015 (Directive), whichever is the earliest.

Question: Can I introduce a pharmacovigilance system master file for my authorised medicinal product(s) in advance of the deadline set out in the legislation?

For medicinal products for which a marketing authorisation was granted before 2 July 2012 (Regulation) / 21 July 2012 (Directive), a pharmacovigilance system master file (PSMF) should be in place either at the time of the date of renewal or by 2 July 2015 (Regulation) /21 July 2015 (Directive), whichever is the earliest.

However, marketing authorisation holders may introduce on a voluntary basis a pharmacovigilance system master file at an earlier stage in the period between July 2012 and July 2015 provided the marketing authorisation holder's PSMF fully complies with the requirements of the implementing measure for the PSMF.

In order to do so a marketing authorisation holder would be required to submit a variation request to switch from the detailed description of the pharmacovigilance system in the marketing authorisation to the summary of the pharmacovigilance system. The classification of the variation will either follow published guidelines or if unforeseen at the time of submission the appropriate procedures (cf. Article 5 of Regulation (EC) No 1234/2008).

Question: When I introduce a pharmacovigilance system master file for my authorised medicinal product(s) outside the renewal process, will this be considered as a variation? Does it make a difference whether competent authorities already hold a detailed description of the pharmacovigilance system or no specific pharmacovigilance information on the medicinal product(s) concerned? [New July 2012]

Marketing authorisations granted under previous legislation will either contain a detailed description of the pharmacovigilance system (DDPS) or no specific pharmacovigilance system information.

Once a marketing authorisation holder of those marketing authorisations switches to the new system, ie. the PSMF, in accordance with Article 2(1) of Directive 2010/84/EU or Article 3(1) of Regulation (EU) 1235/2010, the marketing authorisation holder needs to:

- either replace the existing detailed description of the pharmacovigilance system by a summary of the pharmacovigilance system in accordance with Article 8(3)(ia) of Directive 2001/83/EC; or

- if a DDPS does not exist, supplement the documentation held by the competent authorities by submitting a summary of the pharmacovigilance system in accordance with Article 8(3)(ia) of Directive 2001/83/EC,

so as to reflect the current system in place. From a public health point of view it is essential that the information the competent authority holds refers to the pharmacovigilance system that is currently used. The summary referred to in Article 8(3)(ia) of Directive 2001/83/EC contains information regarding the qualified person for pharmacovigilance as well as a reference to the location where the pharmacovigilance system master file is kept and the statement that the marketing authorisation holder has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

In accordance with Article 2 of Regulation (EC) 1234/2008 amendments to the information referred to in Article 8(3) of Directive 2001/83/EC are considered as a variation.

4. RISK MANAGEMENT PLAN

Question: In case my medicinal product already operates a risk management plan, do I have to continue to operate it?

Yes, where a marketing authorisation has been granted with an existing risk management plan before 2 / 21 July 2012, the marketing authorisation holder shall continue to operate and maintain the risk management plan.

5. INVOLVEMENT OF THE PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE (PRAC) FOR REFERRALS AND PERIODIC SAFETY UPDATE REPORTS (PSUR)

Question: My PSUR application for a centrally authorised product has been submitted prior to the date of application of the new pharmacovigilance legislation (ie. 2 July 2012), however, the procedure will only be finalised after that date. Will the PRAC be involved?

For centrally authorised products for which PSURs will be submitted before 2 July 2012, the assessment will be carried out by the CHMP without involvement of the PRAC.

Question: My PSUR application for a centrally authorised product has been submitted after the date of application of the new pharmacovigilance legislation (ie. 2 July 2012). Will the PRAC be involved and will the decision making process follow the new rules?

For centrally authorised products for which PSURs will be submitted on or after 2 July 2012, the PSUR procedure will be processed under the new rules with the involvement of the PRAC.

Question: My medicinal product is involved in an Article 31 or 107 or 20 or 36 procedure which has started prior to the date of application of the new pharmacovigilance legislation however, the procedure will only be finalised after that date. Will the PRAC be involved?

For Article 31 and 107 procedures for which notifications will be received before 21 July 2012, the matter is assessed and finalised by the CHMP, without requiring PRAC and CMD(h) involvement.

For Article 20 procedures for which notifications will be received before 2 July 2012, the matter is assessed and finalised by the CHMP, without requiring PRAC involvement.

For Article 36 procedures still on-going on 21 July 2012, the matter will continue to be assessed and finalised by the CHMP and the Commission in accordance with Articles 32, 33 and 34 of Directive 2001/83/EC.

Question: My medicinal product is involved in an Article 31 or 107i or 20 procedure which has started after the date of application of the new pharmacovigilance legislation. Will the PRAC be involved and will the decision making process follow the new rules?

For Article 31 and Article 107(i) procedures for which notifications will be received on or after 21 July 2012, the referral procedure will be processed under the new rules, which includes the involvement of the PRAC in cases that are based on the evaluation of data resulting from pharmacovigilance activities.

For Article 20 procedures for which notifications will be received on or after 2 July 2012, the procedure will be processed under the new rules, which includes the involvement of the PRAC in cases that are based on the evaluation of data resulting from pharmacovigilance activities.

6. POST-AUTHORISATION SAFETY STUDIES

Question: I have the obligation to conduct a non-interventional post-authorisation safety studies (PASS) imposed as a condition to my marketing authorisation. If I have to submit the protocol, amendments and final study results after the application of the new pharmacovigilance legislation (ie. 2 July 2012 for centralised procedure applications and 21 July 2012 for national applications), do the procedures as set out in Articles 107n to 107q of Directive 2001/83/EC apply to my PASS?

For non-interventional post-authorisation safety studies imposed in accordance with Articles 21a and 22a of Directive 2001/83/EC and Articles 10 and 10a of Regulation (EC) No 726/2004, the procedures provided for in Articles 107n to 107q of Directive 2001/83/EC (or Article 28b of Regulation (EC) No 726/2004) apply only to PASS studies which have been imposed after 2 July/21 July 2012 as a condition to a marketing authorisation.

Therefore if the PASS was imposed as a condition before 2 July 2012 for centralised marketing authorisations and 21 July 2012 for national marketing authorisations, the procedures as set out in Articles 107n to 107q of Directive 2001/83/EC (or Article 28b of Regulation (EC) No 726/2004) do not apply.

7. PERIODIC SAFETY UPDATE REPORTS (PSUR)

Question: Which PSUR cycle should my medicinal product follow for marketing authorisations granted just after 2 / 21 July 2012? [New July 2012]?

Marketing authorisation holders covered by Article 107b of Directive 2001/83/EC or Article 28(2) of Regulation (EC) 726/2004 have to submit periodic safety update reports from the date of authorisation. As set in the new legislation, the frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

For medicinal products for which the application was submitted before 2 / 21 July 2012 but the marketing authorisation was granted in the months following the entry into force of the new legislation, the decision on the granting of the marketing authorisation may

not yet specify the PSUR cycle or include a cross-reference to the list of Union reference dates for periodic safety update reports (EURD list).

The legislation provides rules only for those marketing authorisations which were granted before 2 / 21 July 2012 (Article 107c(2) of Directive 2001/83/EC), and for which the frequency and dates of submission of PSURs are not laid down as a condition to the marketing authorisation. By analogy the same rules should apply for the PSUR cycle of marketing authorisation granted after 21 July 2012 but submitted before that date. Consequently, PSURs shall be submitted to the competent authorities immediately upon request or in accordance with the following frequency:

a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;

b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

This frequency applies until otherwise specified in the EURD list or in the individual marketing authorisation.

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