01 July 2016
EMA/457260/2016
Procedure Management and Business Support

Questions & answers on Article 20 non-pharmacovigilance procedures

This guidance document addresses a number of questions which stakeholders, in particular marketing authorisation holders (MAHs), may have on an Article 20 non-pharmacovigilance procedure. It provides an overview of the European Medicine Agency's (the Agency) practical and operational aspects with regards to the handling of Article 20 non-pharmacovigilance procedures.

This integrated version has been created for printing purposes only. Please refer to the individual questions & answers as published in the referral procedures guidance for access to the hyperlinked information.

Questions and answers are being updated continuously, and will be marked by "NEW" or "Rev." with the relevant date upon application.

Note:

It should be highlighted that this document has been produced for guidance only and should be read in conjunction with "The rules governing Medicinal Products in the European Union, Volume 2A, chapter 3, Notice to applicants".

MAHs must in all cases comply with the requirement of EU legislation.

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Table of contents

Initiation of an Article 20 non-pharmacovigilance procedure

1. What is the legal basis for an Article 20 non-pharmacovigilance procedure?

An Article 20 non-pharmacovigilance procedure follows the provisions of Article 20 of Regulation (EC) No 726/2004.

It applies when the procedure is initiated as a result of the evaluation of data that do not relate to pharmacovigilance activities of medicinal product(s)[1] authorised via the centralised procedure only.

References:

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Notice to Applicants, volume 2A Procedures for marketing authorisation, Chapter 3 Union Referral Procedures (dated May 2014)

2. In which situations can an Article 20 non-pharmacovigilance procedure be initiated?

An Article 20 non-pharmacovigilance procedure should be initiated in case a Member State (MS) or the European Commission (EC) considers that one of the measures envisaged under title IX (Pharmacovigilance) or XI (Supervision and sanctions) of Directive 2001/83/EC must be applied for centrally authorised medicinal products (CAPs), as a result of the evaluation of data that do not relate to pharmacovigilance, for example data relating to the quality or efficacy of a CAP(s).

Reference:

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

3. Who can initiate an Article 20 non-pharmacovigilance procedure?

An Article 20 non-pharmacovigilance procedure can only be initiated by the European Commission (EC). A marketing authorisation holder (MAH) cannot trigger this procedure.

The EC refers the matter to the Agency, by circulating a notification to the Agency and to all Member States (MSs), requesting an opinion by the Committee for Medicinal Products for Human Use (CHMP).

The notification will identify the concern including a detailed explanation of the issue raised and the regulatory action which is being considered.

The notification will be publicly available at the start of the procedure (please refer to Question 6.).

[1] When the procedure is initiated as a result of the evaluation of data relating to the pharmacovigilance activities of centrally authorised medicinal product(s), the procedure for an Article 20 pharmacovigilance referral will apply, and in such cases the matter should be referred to the Pharmacovigilance Risk Assessment Committee (PRAC). Please refer to the Questions & Answers on Article 20 pharmacovigilance referrals.

4. Can a Member State take regulatory action on a centrally authorised medicinal product?

A Member State (MS) may on its own initiative or at the European Commission's (EC) request, where urgent action is considered essential to protect public health, suspend the use of a centrally authorised medicinal product in its territory, until a definitive decision is adopted.

When it does so on its own initiative, the MS should inform the EC, the Agency of the reasons of its action no later than the next working day following the suspension.

The Agency will inform all other MSs without delay, and the EC will immediately initiate an Article 20 non-pharmacovigilance procedure, if not already ongoing.

5. Which medicinal products can be involved in an Article 20 non-pharmacovigilance procedure?

An Article 20 non-pharmacovigilance procedure is initiated where only centrally authorised medicinal products (CAPs) are concerned by the issue.

The procedure may concern one specific medicinal product, all medicinal products containing the same active substance (range of medicinal products) or all medicinal products belonging to the same therapeutic class (several active substances). The CAPs to be included depend on the scope of the procedure.

If the concern referred relates to a range of products or therapeutic class involving not only CAPs but also nationally authorised medicinal products (including products authorised via the mutual recognition and decentralised procedures), then an Article 31 non-pharmacovigilance referral[2], will be initiated including all products affected.

6. When and how will an Article 20 non-pharmacovigilance procedure be announced?

A brief summary of the issue will be discussed at the upcoming Committee for Medicinal Products for Human Use (CHMP) plenary meeting and will be included in the agenda published at the beginning of the CHMP meeting.

The start of the procedure will be announced as part of the CHMP meeting highlights, which will be published on the next working day following the CHMP meeting during which the matter is considered.

The announcement will specify the issue under consideration, the product(s) concerned and will include the publication of the following documents on the Agency's website on the specific procedure webpage:

- announcement of the start of the procedure;
- notification triggering the procedure;
- list(s) of questions and timetable adopted by the CHMP.

The announcement on the Agency's website will also be linked to the European public assessment report (EPAR) of the centrally authorised medicinal product(s) concerned by the Article 20 non-pharmacovigilance procedure.

Reference:

Guide to information on human medicines evaluated by EMA

[2] Please refer to the Questions & Answers on Article 31 non-pharmacovigilance referral.

7. How will marketing authorisation holder(s) be informed about the start of the Article 20 non-pharmacovigilance procedure?

The public announcement on the Agency's website will include information related to the start of procedure.

In addition, all marketing authorisation holder(s) (MAHs) concerned by the Article 20 non-pharmacovigilance procedure will be notified electronically (via email/Eudralink) by the Agency.

The letter notifying MAH of the procedure initiation will include:

- the name and contact details of the Agency's Procedure Manager (PM) from the referral procedures service that will be the primary contact point for this procedure only. The EMA Product Lead for the centrally authorised product will remain assigned to this product and should always be put in copy in all correspondence regarding the Article 20 non-pharmacovigilance procedure;
- the pathway to the Agency's web page where the relevant documentation is available.

The Agency may release updated information on the website during the procedure and therefore MAHs should continuously check the Agency's website for any relevant updates (please refer to Question 27. and Question 31.).

8. Should marketing authorisation holders identify contact person to communicate with the Agency during the Article 20 non-pharmacovigilance procedure?

The marketing authorisation holder's (MAH) designated contact person for each centrally authorised product concerned by the procedure will, by default, be the contact person and will receive all the correspondence from the Agency regarding the Article 20 non-pharmacovigilance procedure.

The MAHs may if they wish to, designate a different contact person for the Article 20 non-pharmacovigilance procedure. In this case they must inform the procedure manager (PM) identified in the letter notifying the procedure initiation.

All documentation concerning the Article 20 non-pharmacovigilance procedure will be sent to the contact person only. Receipt of any documents by the contact person will be considered to constitute effective receipt by the MAH *inter alia* for the purposes of calculating the procedural timelines.

9. Can marketing authorisation holders group with other marketing authorisation holders involved in the procedure?

The marketing authorisation holders (MAHs) can form a group for the purpose of the procedure (irrespective of group/company affiliation) in order to provide a single consolidated response and/or oral explanations to the questions raised by the Committee for Medicinal Products for Human Use (CHMP) during the procedure. In this case the cover letter accompanying the single consolidated response and/or request for oral explanation should clearly identify the parties responsible for the submission/request.

10. Do marketing authorisation holders have to pay a fee?

Currently, no fees are payable for the assessment of an Article 20 non-pharmacovigilance procedure.

11. Who can submit data to be considered for this procedure?

The marketing authorisation holder(s) (MAHs) concerned by an Article 20 procedure will be requested to submit information relevant for the assessment of the concern.

This is an opportunity given to the MAHs to present written or oral explanations to the Committee for Medicinal Products for Human Use (CHMP) within the time limit as specified in the procedure timetable, before an opinion is issued by the CHMP.

For detailed information on how and when to submit data please refer to Question 15 and Question 17.

Regardless of whether or not the MAHs present written or oral explanations to the CHMP, an opinion will be issued by the CHMP in any case, applicable to all marketing authorisation(s) concerned by the procedure.

12. How will data be gathered during the procedure?

The concern triggering the Article 20 non-pharmacovigilance procedure will be substantiated by additional data that could be requested by the Committee for Medicinal Products for Human Use (CHMP) in the format of a list(s) of questions/list of outstanding issues, comments on the scientific background supporting the triggering of the procedure or by using data sources available to the Agency and/or to the national competent authorities (NCA) of the Member States (MSs).

The data to be considered for the assessment will have to be submitted within the specified deadline. as published in the announcement of the start of the procedure (please refer to Question 6.).

Notwithstanding the above, the CHMP may also collect additional data through a further list of outstanding issues or in an oral explanation in accordance with an extended timetable, which will be made publicly available (please refer to Question 19. and Question 21.).

13. Who will perform the assessment?

The assessment of data within the Article 20 non-pharmacovigilance procedure is carried out by the Committee for Medicinal Products for Human Use (CHMP). At the start of the procedure, the CHMP Chairperson appoints a CHMP rapporteur and CHMP co-rapporteur(s) who will perform the assessment of all data collected within the agreed timelines.

The assessment will result in the CHMP adopting an opinion on the issue reviewed.

14. How are the CHMP rapporteur and CHMP co-rapporteur appointed?

The Committee for Medicinal Products for Human Use (CHMP) (co-)rapporteurs for an Article 20 non-pharmacovigilance procedure is appointed by the CHMP Chairperson from among its members or alternates (hereafter referred to as CHMP members).

If one centrally authorised medicinal product (CAP) is involved, the CHMP (co-)rapporteurs already nominated for the CAPs are appointed.

If more than one CAP is involved, the CHMP (co-)rapporteurs for the Article 20 procedure shall be appointed from amongst the CHMP (co-)rapporteurs for the CAPs involved in the procedure. In case the procedure is not product specific, the CHMP Chairperson may advise to open rapporteurship to all CHMP members.

In case of an Article 20 procedure concerning several medicinal products belonging to the same therapeutic class or where several issues are to be assessed, a lead rapporteur and several co-rapporteurs could be appointed.

The CHMP Chairperson will endeavour to apply the criteria of best available expertise to be taken into account for the appointment of the CHMP (co-)rapporteurs for each procedure.

Reference:

Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology in accordance with Article 62(1) of Regulation (EC) No 726/2004

During the assessment

15. How shall I present my answers?

Marketing authorisation holder(s) (MAHs) should submit to the Agency and all Committee for Medicinal Products for Human Use (CHMP) members all available evidence to support the matter relating to the procedure in response to the List of Question and as per the timelines published on the Article 20 non-pharmacovigilance procedure webpage.

The MAHs of products concerned by the procedure should submit their responses as follows:

- The data should be presented in electronic format in accordance with the electronic Common Technical Document (eCTD) format and accompanied by a signed cover letter and a written summary of each question.
- The cover letter must make clear reference to the procedure number and the Agency's procedure manager (PM) from the referral procedures service should always be put in copy. A cover letter template can be found here.
- The written summary answering each question should follow the numbering as per the CHMP list of questions and CHMP list of outstanding issues. Please note that supportive data to the responses submitted (e.g. study reports, literature data) are expected to be provided together with a summary of those data as per the modular structure of the eCTD format.

Published data can be presented as supportive documentation in response to a specific question if no other data is available.

In case some questions (e.g. on a specific pharmaceutical form) are not applicable/relevant to all the product(s) concerned by the procedure, or to the product(s) of the represented group, the response should be "not applicable" with a short explanation.

It should be noted that the responsibility for the quality of the submitted documentation lies with the MAHs and is crucial to the overall assessment. All submissions are expected to be submitted in English and electronically only (please refer to Question 17).

Submission of responses for centrally authorised products should follow the dossier requirements for centrally authorised products (please refer to Question 17).

In case MAHs formed a group (please refer to Question 9), the cover letter accompanying the single consolidated response and/or request for oral explanation should clearly identify the parties responsible for the submission/request.

16. When do I have to submit revised product information?

In case the answers to the Committee for Medicinal Products for Human Use (CHMP) require changes to the product information, the marketing authorisation holder(s) (MAHs) must submit the revised product information annexes as part of the responses. Only the English language version (highlighted version) of a relevant example of the full set of product information annexes (i.e. Annex I, II, IIIA and IIIB) is required during the assessment.

17. How and to whom shall I submit my responses?

Responses from marketing authorisation holder(s) (MAH) should be submitted to the Agency within the timeline specified on the procedure webpage.

All submissions for referral procedures should be sent via the eSubmission Gateway and/or the Web Client. These portals send automated acknowledgement of receipt of submission, or of failed submission if an error occurred. The Agency no longer accepts submissions on CD-ROM or DVD.

Please note that all submissions for CAPs in eCTD format are available via the Common Repository and will be considered delivered to all National Competent Authorities' (NCAs) representatives, alternates and scientific experts. Additional copies of submissions should not be sent directly to the NCAs on CD/DVD or via CESP as this might lead to validation issues and cause delays.

CAP referral submissions should always be submitted individually as the next sequence in the product lifecycle of each CAP. Standalone eCTD submissions for the active substance are not allowed for CAPs included in referral procedures. Detailed information on the required naming conventions and file formats can be found in detailed examples of filenames for different application types and in the eSubmission gateway web client - guidance for applicants. For more information please refer to eSubmission website.

For advanced therapy medicinal product (ATMP), additional submission requirements apply, please refer to the dossier requirements for centrally authorised products.

18. How will my data be assessed?

Submissions from the marketing authorisation holder(s) (MAHs) are provided directly to the Committee for Medicinal Products for Human Use (CHMP) (co-)rapporteurs to be considered in their assessment.

All information gathered will be assessed within an agreed timeframe as published on the Article 20 non-pharmacovigilance procedure webpage. The assessment report(s) prepared by the CHMP (co-)rapporteur will reflect all data reviewed and considered for the assessment.

The CHMP (co-)rapporteur's assessment report(s) will be circulated to the CHMP members for comments.

19. What is the timetable for the assessment by the Committee for Medicinal Products for Human Use?

Please note that the timelines below are provided for guidance purposes only and refer to active days, which correspond to the time the Committee for Medicinal Products for Human Use (CHMP) takes to assess the data provided.

The timelines following a 60 day assessment period are as follows:

Article 20 non-pharmacovigilance procedure – *Timetable for the assessment*	Day
Notification of a start of procedure to the CHMP/Agency secretariat	Day 0
Discussion at the first meeting of the CHMP following receipt of the notification: • Discussion of the question(s) referred during the plenary meeting and whether an oral explanation(s) should be held • Appointment of the CHMP (co-)rapporteurs • Adoption of the CHMP list of questions (LoQ) to be addressed by the marketing authorisation holder(s) (MAHs) and timetable	Day 1
Preparation and submission of written explanations by the MAH(s) in response to the CHMP list of questions	Clock Stop
Re-start of the procedure following submission of the responses in accordance with procedural timetables	Clock re-start
Circulation of the CHMP (co-)rapporteur's assessment report(s) on the MAH(s)' written responses	Day 20
Comments in writing on the CHMP (co-)rapporteurs' assessment report(s) from CHMP members	Day 25
Discussion at the CHMP meeting: • Adoption of the CHMP opinion, or • Adoption of CHMP list of outstanding issues (LoOI) to be answered in writing and/or in an oral explanation and timetable for the next assessment period of the procedure	Day 30
Preparation and submission of written and/or oral explanations (if necessary)	Clock Stop
Re-start of the procedure following submission of written explanations (in accordance with the published submission dates) or at the time of oral explanations (if necessary)	Clock re-start Day 31
Discussion at the CHMP meeting: • Adoption of the CHMP opinion	Day 60

The dates to be followed in accordance with the adopted timetable by the CHMP for each month can be found in the following link to procedural timetables.

The above timetable reflects an example where, after the deadline for the submission of all data as published on the procedure webpage, the CHMP conducts its assessment and adopts an opinion in 60 days. However, depending on the urgency, the complexity and amount of data to assess the CHMP may agree on a shorter or longer timetable.

The CHMP may also extend the time limit of 60 days to allow for the assessment of further data provided as answers to the CHMP list of outstanding issues, oral explanation, or in case the CHMP

requires input from a scientific advisory group (SAG) or from an ad-hoc expert group to support the CHMP opinion.

As a general rule, a clock-stop of up to one month will apply. For an extension of the clock-stop adopted by the PRAC, the MAH should send a justified request to the Agency for agreement by the CHMP. The letter specifying the length of the requested extension should be addressed to the CHMP Chairperson, signed and sent electronically to the EMA procedure manager. In preparing the justification, the MAH should consider the seriousness and urgency of the issue under consideration and the impact the extension may have on public health. The CHMP will consider the request, and if agreed, an extended timetable may be adopted. All MAHs involved in the procedure, will be informed of the PRAC outcome.

The CHMP assessment of responses to the list of outstanding issues will take up to 30 or, in exceptional cases, 60 days depending on the complexity and amount of data provided by the MAH(s).

20. Will I receive the CHMP (co-)rapporteur's assessment report(s)?

All marketing authorisation holder(s) with products included in the scope of the Article 20 non-pharmacovigilance procedure will be provided with the Committee for Medicinal Products for Human Use (CHMP) (co-)rapporteur's assessment report(s) via email/Eudralink.

21. Will I have the possibility to present my views in front of CHMP and how is this organised?

The Committee for Medicinal Products for Human Use (CHMP) may decide whether there are issues that need to be addressed orally by the marketing authorisation holder(s) (MAHs). In such a case the MAH(s) will be duly informed in advance on the issues to be addressed during an oral explanation.

The MAH(s) may also make a request to the CHMP to attend an oral explanation. In such a case, the MAH(s) should send a written request to the CHMP stating the reason(s) and specifying the issue(s) to be addressed during the oral explanation. The CHMP will take due account of the request and will decide whether the oral explanation will be held.

Oral explanation(s) should take place during the assessment phase and after the receipt of the CHMP (co-)rapporteur's assessment report(s). Further detailed information on organisational aspects of the oral explanation can be found here.

The MAH(s) can provide the oral explanation on their own behalf or on behalf of the group of MAHs whom they represent.

22. What should I do if my product is withdrawn or transferred to another marketing authorisation holder?

If during the procedure, the marketing authorisation (MA) for a centrally authorised product (CAP) is withdrawn or transferred, the former marketing authorisation holder (MAH) should inform the Agency and the appropriate procedure should be followed (please refer to withdrawn-product notification: questions and answers and transfer of marketing authorisation: questions and answers).

23. What should I do if the name of my product changes or, if the name or address of the marketing authorisation holder changes?

If during the procedure, the name of a medicinal product (CAP) is changed, or the name and/or address of a marketing authorisation holder (MAH) changes, the marketing authorisation holder (MAH)

should inform the Agency and the appropriate procedure should be followed (please refer to changing the (invented) name of a centrally authorised medicine: questions and answers).

Committee for Medicinal Products for Human Use (CHMP) opinion

24. What is the basis of the Committee for Medicinal Products for Human Use opinion?

In order for the Committee for Medicinal Products for Human Use (CHMP) to reach an opinion, the CHMP considers available data in relation to the matter referred to. The CHMP can take into account quality, pre-clinical and clinical data (including data from clinical trials) and published literature. This data can be provided by the marketing authorisation holder(s) (MAHs) and/or by the Member States (MS)/Agency. In certain cases the CHMP can also consult experts in specific fields (e.g. through CHMP ad-hoc expert or scientific advisory (SAG) group meeting).

25. What could be the outcome of the Committee for Medicinal Products for Human Use opinion?

The Committee for Medicinal Products for Human Use (CHMP) opinion on the Article 20 non-pharmacovigilance procedure may be that:

a) the marketing authorisation(s) (MAs) should be maintained or varied;

b) the MAH(s) should be subject to certain conditions (in case of maintenance or variation);

c) the MA(s) should be suspended or revoked.

Where the opinion is for the MA(s) to be varied, including changes or addition of information in the summary of the product characteristics (SmPC), labelling or package leaflet (PL), the opinion will include the suggested wording of such changes or added information, and state where in the SmPC, labelling or PL such wording should be placed.

Where the CHMP recommends that the MA(s) should be subject to certain conditions, these can include, but are not limited to, requesting the marketing authorisation holder(s) to conduct a post-authorisation study.

The CHMP opinion can be adopted either by consensus or by majority vote. In the event of adoption by majority, the divergent positions of the concerned CHMP members and the grounds on which they are based will be appended to the opinion issued by the CHMP.

26. How is the CHMP opinion structured?

The Committee for Medicinal Products for Human Use (CHMP) will include:

- a cover page in which the adopted CHMP opinion is outlined together with the voting outcome of the CHMP;
- the listing of all products concerned i.e. the respective Annex A for each product will be attached;
- the scientific grounds and explanation for the CHMP opinion;

- the revised product information (in English only) with agreed wording included in the relevant sections of the summary of product characteristics and/or the labelling and/or package leaflet, if applicable;
- the conditions or restrictions imposed to the marketing authorisation for the safe and effective use of the medicinal product, if applicable;
- the CHMP member(s)'s divergent views, in case the opinion is adopted by majority;
- the CHMP assessment report on the evaluation performed and the conclusion of the CHMP that led to the adoption of the opinion based on all data gathered;
- the Direct Healthcare Professional Communication (DHPC) and communication plan as agreed by CHMP, if applicable.

27. When will the CHMP opinion be published?

A brief outcome of the Committee for Medicinal Products for Human Use (CHMP) opinion will be included in the meeting highlights that are released the next working day following the plenary meeting, together with an EMA public health communication (including a summary of the CHMP opinion and targeted information for healthcare professional and patients) and, if applicable, the wording to be included in the product information.

The CHMP opinion will be published on the procedure webpage following the adoption of the European Commission Decision (please refer to Question 31.).

Reference:

Guide to information on human medicines evaluated by EMA

28. Will I receive the CHMP opinion?

The marketing authorisation holder(s) of products concerned and identified at the start of the procedure will receive the Committee for Medicinal Products for Human Use (CHMP) opinion during the week following the meeting when the opinion was adopted**.**

29. When do I have to submit the translations?

The marketing authorisation holder(s) of centrally authorised products (CAPs) involved in the procedure will have to provide the full product information in all EU languages by Day +5 (i.e. 5 days after adoption of the opinion) to the Member States' (MSs) contact points for linguistic check and copied to the Agency. Member states may send linguistic comments until Day +19. The MAH(s) should send the translations amended accordingly together with the completed QRD form 2 to the Agency by Day +25.

Further detailed information on the translation process of Committee for Medicinal Products for Human Use (CHMP) opinion can be found here.

30. What happens after the Committee for Medicinal Products for Human Use opinion?

After the Committee for Medicinal Products for Human Use (CHMP) opinion, the Agency together with the concerned marketing authorisation holder(s) (MAHs) and national competent authorities (NCAs) in

the Member States (MSs) will finalise the translations and will send these to the European Commission (EC).

The EC will then start the decision-making process leading to the adoption of a binding decision addressed to the MAH(s).

Detailed information on the decision-making process can be found here.

The MAHs need to submit within 5 days following the EC decision, an eCTD closing sequence of the final documents.

31. Will there be any publication in relation to the Article 20 non-pharmacovigilance procedure after the Commission Decision?

Around one week following the adoption of the European Commission (EC) decision, the Committee for Medicinal Products for Human Use (CHMP) assessment report will be published on the procedure webpage. Within four weeks of the adoption of the EC decision, the CHMP Opinion with its annexes in all EU languages will also be published on the procedure webpage, which will be updated to reflect the date of the EC decision. In addition, this page will be linked to the European public assessment report (EPAR) of the centrally authorised medicinal product(s) concerned by the Article 20 procedure.

Reference:

Guide to information on human medicines evaluated by EMA