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Questions & answers on Article 31 non-pharmacovigilance referrals

This guidance document addresses a number of questions which stakeholders, in particular the marketing authorisation holders (MAHs)/applicants, may have on an Article 31 non-pharmacovigilance referral procedure. It provides an overview of the European Medicines Agency's (the Agency) practical and operational aspects with regards to the handling of Article 31 non-pharmacovigilance referral 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 to access the hyperlinked information.

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

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, chapter3, Notice to applicants".

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

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Initiation of an Article 31 non-pharmacovigilance referral

1. What is the legal basis of an Article 31 non-pharmacovigilance referral?

An Article 31 non-pharmacovigilance referral follows the provisions of Article 31 of Directive 2001/83/EC.

It applies where the interests of the European Union are involved, and when the procedure is initiated as a result of the evaluation of data other than data relating to the pharmacovigilance[1] of authorised medicinal product(s) or application(s).

The procedure for an Article 31 non-pharmacovigilance referral is laid down in Articles 32, 33 and 34 of Directive 2001/83/EC.

References:

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

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

2. In which situations can an Article 31 non-pharmacovigilance referral be initiated?

An Article 31 non-pharmacovigilance referral should be initiated where the interests of the Union are involved as a result from the evaluation of data that do not relate to pharmacovigilance activities, for example data relating to the quality and/or efficacy of an authorised medicinal product(s) or application(s)[1]. In such cases the matter will be referred to the Committee for Medicinal Products.

The term 'interest of the Union' refers particularly to the interests of public health related to medicinal products in the Union (for example in light of concerns related to the quality and efficacy of a medicinal product) and to the free movement of products within the Union.

3. Who can initiate an Article 31 non-pharmacovigilance referral?

An Article 31 non-pharmacovigilance referral procedure can be initiated by the competent authorities in the Member States (MSs), the European Commission (EC) or by the marketing authorisation holders (MAHs) and/or applicants.

The initiator of the procedure refers the matter to the Committee for Medicinal Products for Human Use (CHMP) by circulating a notification to the Agency, all MSs and the EC.

The notification will identify the concern and question(s) referred to the CHMP for consideration. The notification will also include a detailed explanation of the issue raised, and should address how the Union interests are involved.

Only the MS concerned or the EC can identify the question. Therefore in advance of initiating a referral under this Article, the MAH/applicant should contact a MS or the EC with a request to assess and

[1] When the procedure is initiated as a result of the evaluation of data relating to the pharmacovigilance activities of authorised medicinal product(s), the procedure for an Article 31 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 31 pharmacovigilance referrals.

confirm the Union interest. The MAH/applicant can include in the scope of the referral only its own product, with justification of potential extension to others.

The notification will be publicly available at the start of the procedure (please refer to Question 8).

4. Can a Member State take regulatory action during an Article 31 non-pharmacovigilance referral?

A Member State (MS) may, where urgent action is necessary to protect public health, suspend the marketing authorisation at any stage of the procedure, and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted.

In this case, the MS informs the European Commission (EC), the Agency and all other MSs, no later than the following working day, of the reasons for its action.

5. Which medicinal products can be involved in an Article 31 non-pharmacovigilance referral?

All medicinal products affected by the concern and with a valid marketing authorisation (MA) in the European Economic Area (EEA) will be included in the Article 31 non-pharmacovigilance referral. This includes all medicinal products affected by the concern, regardless of whether the MA was granted nationally (including via the mutual recognition and decentralised procedures) or via the centralised procedure. Applicants of MAs may also be included. However, in case the issue concerns only centrally authorised medicinal products (CAPs), the procedure under Article 20 of Regulation (EC) No 726/2004[2] is initiated instead.

The referral procedure may concern a 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 concerned).

The marketing authorisation holders (MAHs)/applicants cannot choose whether or not to include their medicinal products in an Article 31 non-pharmacovigilance referral. The inclusion of their medicinal products depends on the scope of the procedure.

Reference:

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

6. How are the medicinal products identified to be part of an Article 31 non-pharmacovigilance referral? Rev. Jan 2017

The Agency, with input from the competent authorities of the Member States (MSs) within the European Economic Area (EEA) as necessary, will identify the authorised medicinal products or the applicants concerned by the procedure. Whenever possible, all authorised medicinal products concerned are identified using information from the Article 57 database. This will take place before the start of the procedure and a draft list of the medicinal products identified will be publically available on the Agency's website on the specific procedure webpage (please refer to Question 8).

[2] Please refer to the Questions & Answers on Article 20 non-Pharmacovigilance procedures.

If after consultation with the MSs it is concluded that the issue also concerns other medicinal product(s) (e.g. range of medicinal products, a therapeutic class) than the ones covered by the notification, the Agency can extend the scope of the procedure.

From a procedural view point, only those medicinal products identified at the start of the procedure will be covered by its scope. However, to the extent that other medicinal products affected by the concern that triggers the Article 31 referral but not identified at start of procedure are authorised in the EEA, or subject to future authorisations by the MSs, the concerned MSs should take due consideration of the scientific conclusions of the procedure and apply them to these products.

7. What happens if the medicinal product involved is only authorised in one Member State? Rev. Jan 2017

Upon receipt of the notification, the Agency, based on the information collected from the Article 57 database and, as necessary, in consultation with the national competent authorities (NCAs) of the Member States (MSs) within the European Economic Area (EEA), will identify in which MS(s) the concerned medicinal product(s) is/are authorised.

If it is concluded that the scope of the procedure concerns medicinal product(s) authorised in only one MS and the interest of the EU is not involved, an Article 31 non-pharmacovigilance referral procedure will not be initiated and the concern will be handled by the MS concerned.

8. When and how will an Article 31 non-pharmacovigilance referral be announced?

The issue will be discussed at the upcoming Committee for Medicinal Products for Human Use (CHMP) plenary meeting and a brief summary 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 concern under consideration 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;
- draft list of concerned medicinal products/active substance and MAHs/applicants;
- list(s) of questions and timetable adopted by the CHMP.

Reference:

Guide to information on human medicines evaluated by EMA

9. How will the marketing authorisation holders/applicants be informed of the start of the Article 31 non-pharmacovigilance referral? Rev. Jan 2017

Whenever possible and when the regulatory contact point for the MAH/applicant can be identified, MAHs will be informed on the Wednesday before the CHMP meeting of new non-pharmacovigilance Article 31 procedures that the CHMP will consider the following week. This communication will be provided for information only.

Following the CHMP meeting, a public announcement on the Agency's website will include information related to the start of procedure.

In addition, all MAHs/applicants of a product(s) concerned by the Article 31 non-pharmacovigilance referral will be notified electronically (via e-mail/Eudralink) by the Agency. The notification of the procedure initiation to the MAHs/applicants will include:

- the name and contact details of the Agency's procedure manager who will be the primary contact point during the procedure, and the address of the product-shared mailbox, which should be copied in all correspondence with the Agency;
- the pathway to the Agency's webpage where the relevant documentation is available.

The Agency may release updated information on the website during the procedure and therefore the marketing authorisation holder(s)/applicants should continuously check the Agency's website for any relevant updates (please refer to Question 29 and Question 34).

10. Should marketing authorisation holders/applicants identify a contact person to communicate with the Agency during the Article 31 non-pharmacovigilance referral? Rev. Jan 2017

The regulatory contact point identified by the marketing authorisation holder (MAH) in the Eudravigilance registration system will, by default, be the contact person and will receive all correspondence from the Agency regarding the Article 31 non-pharmacovigilance procedure. In cases where the concerned products or applications cannot be identified using information in the Article 57 database, the Agency will liaise with the National Competent Authorities to identify the concerned products and corresponding contact person.

The MAHs/applicants may, if they wish to, either designate a different contact person for the procedure within the organisation of the MAH/applicant or be represented by another party. In these cases, they must inform the Agency's procedure manager. The MAH/applicant must ensure that anyone designating a different contact person for the procedure on behalf of the MAH/applicant has the legal authority to do so.

All documentation concerning the Article 31 non-pharmacovigilance referral will be sent only to the contact person as discussed above. Receipt of any documents by the contact person will be considered to constitute effective receipt by the MAH/applicant *inter alia* for the purposes of calculating the procedural timelines.

11. Can I group with other marketing authorisation holders/applicants involved in the procedure?

The marketing authorisation holders (MAHs)/applicants 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.

12. What happens if centrally authorised products are involved in the procedure?

If a centrally authorised product (CAP) is involved in an Article 31 non-pharmacovigilance referral the marketing authorisation holder (MAH) will be notified by the Agency of the start of the procedure as will be all the other concerned MAHs/applicants (please refer to Question 9). The announcement on the Agency's website will also be linked to the EPAR page of the product.

13. Do marketing authorisation holders / applicants have to pay a fee?

Fees are payable only for non-pharmacovigilance referrals under Article 31 of the Directive 2001/83/EC, which have been initiated by the marketing authorisation holder (MAH) or applicant.

References:

Fees payable to the European Medicines Agency

Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products

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

The marketing authorisation holders (MAHs)/applicants concerned by Article 31 non-pharmacovigilance referral procedure will be requested to submit information relevant for the assessment of the concern.

This is an opportunity given to the MAHs/applicants 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 18 and Question 19).

Regardless of whether or not the marketing authorisation holder or applicant has presented written or oral explanations to the CHMP, an opinion will be issued by the CHMP in any case, applicable to all marketing authorisations concerned by the procedure.

15. How will data be gathered during the procedure?

The concern triggering the Article 31 non-pharmacovigilance referral 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 of questions, 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 (NCAs) of the Member States (MSs).

The additional data may be gathered from several different sources (i.e. from concerned marketing authorisation holders (MAHs), healthcare professionals, patients' organisations, Eudravigilance data, data available to the NCAs, etc.).

The need for specific data to be collected is identified by the CHMP at the start of the procedure.

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 8).

Notwithstanding the above, the CHMP may also collect additional data through further lists of outstanding issues and/or an oral explanation in accordance with an extended timetable, which will be made publically available (please refer to Question 21 and Question 23).

16. Who will perform the assessment?

The assessment of data within the Article 31 non-pharmacovigilance referral is the responsibility of the Committee for Medicinal Products for Human Use (CHMP). At the start of the procedure, the CHMP Chairperson appoints a rapporteur and 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.

17. How are the rapporteur and co-rapporteur appointed?

The Committee for Medicinal Products for Human Use (CHMP) (co-)rapporteurs for an Article 31 non-pharmacovigilance referral is appointed by the CHMP Chairperson from amongst 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 31 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 31 non-pharmacovigilance referral concerning several active substances belonging to the same therapeutic class, or where several issues are to be assessed, a lead rapporteur and several (co-)rapporteurs may 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 (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

18. How shall I present my responses? Rev. Jan 2017

Marketing authorisation holders (MAHs)/applicants should submit to the Agency and all Committee for Medicinal Products for Human Use (CHMP) members all available evidence to support the assessment of the impact of the concern being reviewed in the procedure in response to the List of Question and as per the timelines published on the Article 31 non-pharmacovigilance procedure webpage.

MAHs of medicinal products concerned by the referral should submit their responses as follows:

- The data should be presented in electronic format according to the electronic Common Technical Document (eCTD)/CTD 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 should always be put in copy. A table template to complete and insert in the cover letter can be found here.
- The written summary answering each question should follow the numbering as per the CHMP list of questions/CHMP list of outstanding issues (if applicable). Please note that supportive

data to the responses submitted (e.g. study reports, literature data, risk management plan) are expected to be provided together with a summary of those data as per the modular structure of the CTD 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 medicinal products concerned by the procedure, or to the medicinal product(s) of the represented group, the response should be stated as "not applicable" with a short explanation.

It should be noted that the responsibility for the quality of the submitted documentation lies with the MAHs/applicants and is crucial to the overall assessment. The data presented in the submissions should be intended exclusively for the purposes of the concerned procedure. The information and data contained in the individual submissions will be assessed and reflected in the assessment reports related to the concerned procedure. As a general rule, such information and data will not be redacted from the assessment reports with respect to individual products prior to sharing them with all concerned MAHs/applicants. This is based on the fact that the legal principle of transparency and respect of the right of defence requires the Agency to share all relevant information and data that is relevant for the scientific assessment with all concerned MAHs/applicants. Neither the Agency nor the MAHs/applicants can use the information and data contained in the submissions for any other purposes than those related to the concerned procedure. Moreover in general, it is not expected that individual submissions by the MAHs/applicants will include commercially confidential information.

All submissions are expected to be submitted in English and electronically only (please refer to Question 19). Submission of responses concerning the Article 31 Pharmacovigilance referral with regards to centrally authorised products (CAPs) should follow the requirements for post-authorisation procedures for CAPs (e.g. submission via e-CTD).

In case MAH(s) formed a group (please refer to Question 11) the cover letter accompanying the single consolidated response and/or request for oral explanation should clearly identify the parties responsible for the submission/request.

19. How and to whom shall I submit my responses? Rev. Sep 2018

Responses from the marketing authorisation holders (MAHs) should be submitted within the timeline specified on the procedure web page.

All submissions for referral procedures should be sent via the eSubmission Gateway or eSubmission Web Client. These portals send automated acknowledgement of receipt of submission, or of failed submission if an error occurred. Responses for nationally authorised products (NAPs) and for centrally authorised products (CAPs) submitted via these portals are available in the common repository and will be considered delivered to all Committee members and alternates.

The Agency no longer accepts submissions on CD-ROM or DVD. Additional copies of submissions should not be sent directly to the NCAs on CD/DVD or via common European submission portal (CESP) as this might cause delays in processing the submissions.

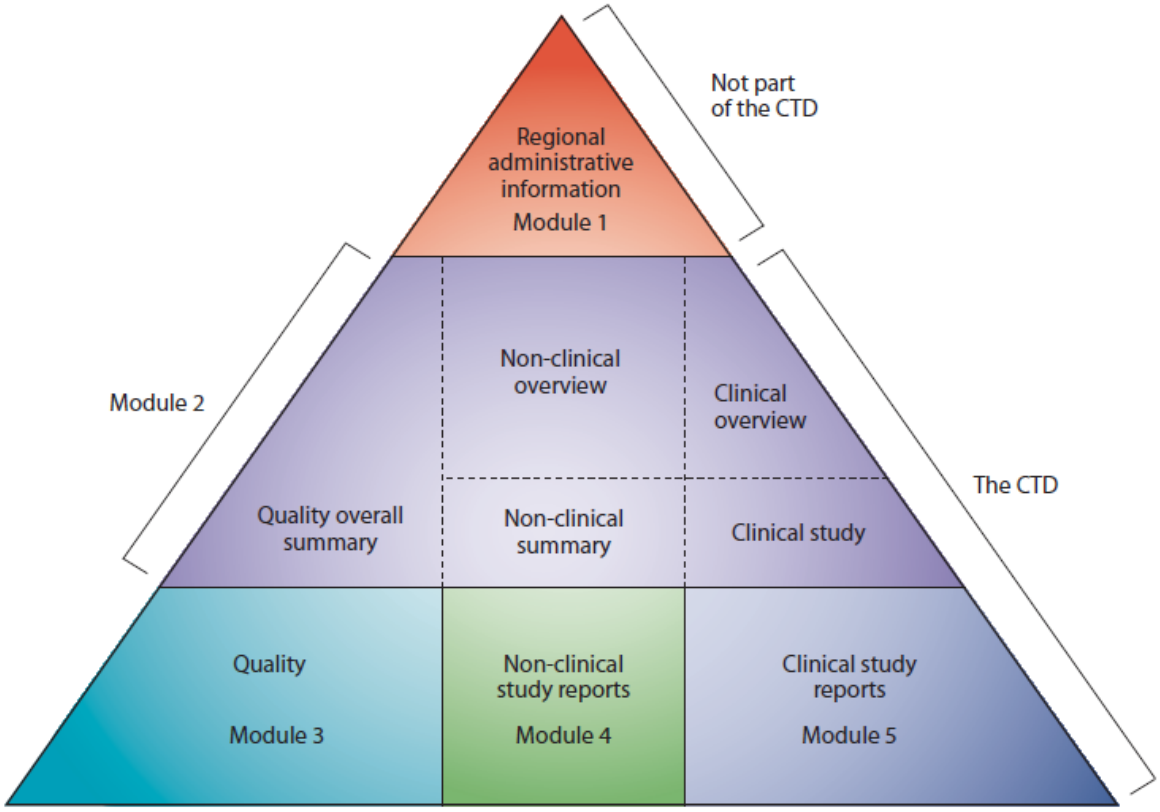
For advanced therapy medicinal product (ATMP), additional submission requirements apply, please refer to the dossier requirements for centrally authorised products.

The Agency strongly recommends using the electronic Common Technical Document (eCTD) or Non-eCTD electronic Submissions (Nees) formats for submissions related to referrals. For referral submissions related to CAPs, it is mandatory to use the eCTD format. It is not possible to submit a

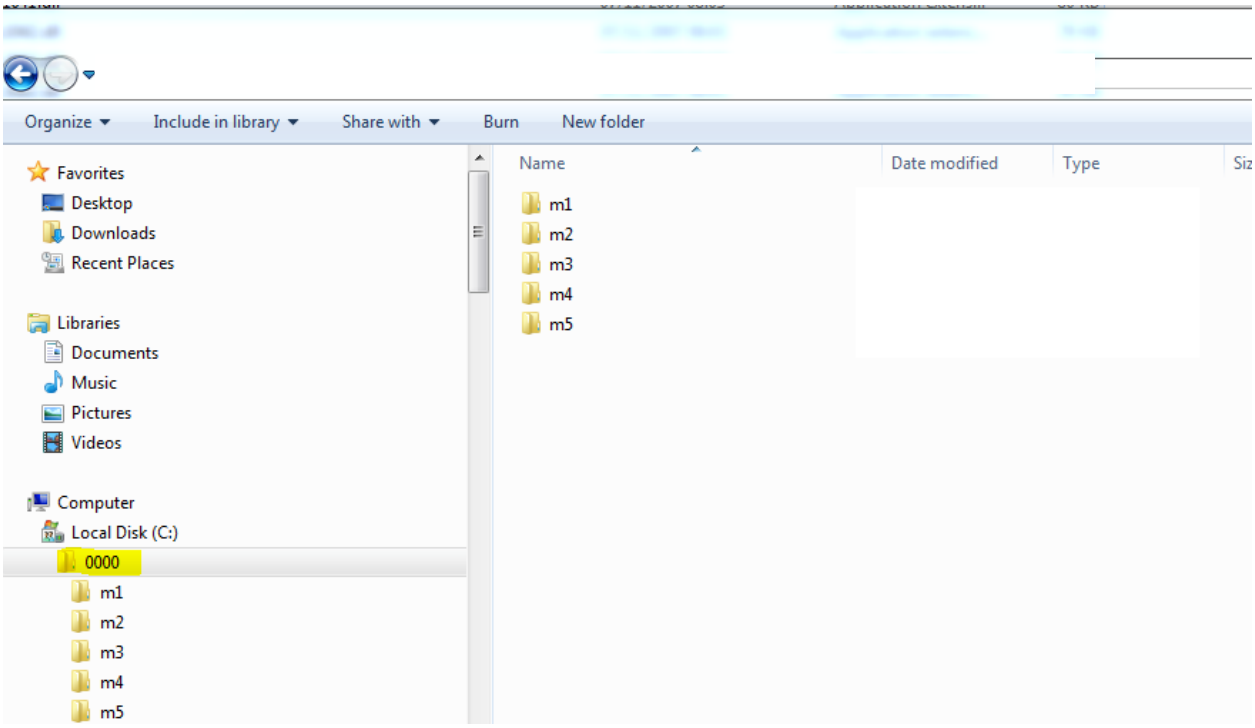
standalone joint eCTD for the CAPs concerned. Responses should always be submitted individually as the next sequence in each CAP product lifecycle. However for submissions related to NAPs, if the documentation is common to several medicinal products and/or MAHs, a single joint eCTD should be submitted. Additional copies of the same eCTD should not be submitted.

For all types of submissions, responses should be presented in the modular format.

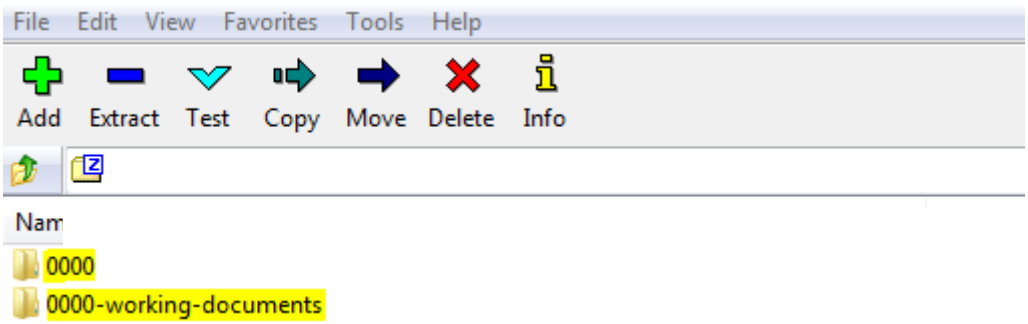
Recommended folder structure:



Documentation can be included in respective modules following the CTD location as referenced in the recommended folder structure, further, root folder should be 4 digits (between 0000-9999), e.g. submission 0000 as below:



Any working documents (for example: documents in Word format) should be outside the root submission folder, e.g. as following:



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.

There is no need to send separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

Should you have any questions regarding your submission, please contact us via email: AskEMA, for any technical issues visit the EMA Service Desk portal.

References:

Dossier requirements for centrally authorised products
Dossier requirements for referral procedures and nationally authorised products

20. How will my data be assessed?

Submissions from the marketing authorisation holders (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 31 non-pharmacovigilance referral webpage. The assessment report(s) prepared by the CHMP (co-)rapporteurs will reflect all data submitted and considered relevant for the review.

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

21. What is the timetable for the assessment by the CHMP? Rev. Jan 2017

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 days assessment period are as follows:

Article 31 non-pharmacovigilance referral – *Timetable for the assessment*	Active day
Notification of a referral 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/confirmation of the CHMP (Co-)rapporteurs • Adoption of the CHMP list of questions (LoQ) to be addressed by the marketing authorisation holders (MAHs)/applicants and timetable	Day 1
Preparation and submission of written explanations by the MAHs/applicants 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 MAHs'/applicants' written responses	Day 20
Comments in writing on the (co-)rapporteur's assessment report(s) from CHMP members	Day 25
Discussion at the CHMP meeting: • Adoption of 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

The dates to be followed in accordance with the adopted timetable by the CHMP for each month can be found here.

The CHMP may extend the time limit up to 150 days to allow for the assessment of further data provided as answers to the CHMP list of outstanding issues, in an 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 CHMP, 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 CHMP 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 MAHs.

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

All marketing authorisation holder(s) (MAHs)/applicants with medicinal products included in the scope of the Article 31 non-pharmacovigilance referral will be provided with the Committee for Medicinal Products for Human Use (CHMP) (co-)rapporteur's assessment report(s) electronically via email/Eudralink.

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

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

The MAHs/applicants may also make a request to the CHMP to hold an oral explanation. The MAHs/applicants should then send a written request to the CHMP stating the reason(s) and specifying the issue(s) to be addressed during the oral explanation. In such a case, 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 MAHs/applicants can provide the oral explanation on their own behalf or on behalf of the group of MAHs/applicants whom they represent.

24. What should I do if my product is transferred to another marketing authorisation holder? Rev. Jan 2017

If the marketing authorisation (MA) for a nationally authorised product (including via mutual recognition and decentralised procedures) is transferred during the referral, both the former and the new marketing authorisation holder (MAH) should update the Article 57 database without delay. The new MAH should provide a copy of the transfer decision of the relevant competent authority to the procedure manager for the referral procedure. It may also provide to the procedure manager information on the new contact person for the procedure (please refer to Question 10).

Following receipt of the transfer decision, the Agency will inform the former MAH that they are no longer included in the Article 31 non-pharmacovigilance referral procedure, in relation to the MA transferred.

For a centrally authorised product (CAP), if the MA is transferred during the procedure, the former marketing authorisation holder should inform the Agency and the appropriate procedure should be followed (please refer to transfer of marketing authorisation: questions and answers).

The products listing published at the start of the procedure (please refer to Question 8) will be updated accordingly and republished on the Agency's website on the specific procedure webpage.

25. What should I do if the name of my product changes, if the name or address of the MAH/applicant changes or if my product is withdrawn?

If during the referral procedure, the name of a nationally authorised product (including mutual recognition and decentralised products) changes or if the name and/or address of a marketing authorisation holder (MAH)/applicant, or if the marketing authorisation (MA) is withdrawn, the marketing authorisation holder (MAH)/applicant should update the Article 57 database without delay and inform the procedure manager for the referral procedure. Following confirmation of the change, the Agency will inform the MAH/applicant that the change has been noted.

If the Article 57 database is updated within the next 30 days following the start of the procedure, these changes will be included in the revised products listing that will be republished at day 30 following the start of the procedure. After day 30 the products listing will not be subject to any other changes except in case of transfer of a MA (please refer to Question 24).

For a centrally authorised product (CAP), if during the procedure, the name of the product or the name and/or address of the MAH changes, or if the MA is withdrawn, the former 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 and to withdrawn-product notification: questions and answers).

Committee for Medicinal Products for Human Use (CHMP) opinion

26. When will the CHMP opinion be issued?

The Committee for Medicinal Products for Human Use (CHMP) will issue an opinion on the matter referred under Article 31 within 60 days of the start date of the procedure. The CHMP may extend that period up to 150 days, to take into account all available data as well as any issues addressed by the marketing authorisation holder(s) (MAHs) during an oral explanation and/or input from experts (if any) if needed before issuing an opinion.

The CHMP opinion will usually be adopted on the last day of the CHMP plenary meeting.

27. What could be the outcome of the opinion of CHMP?

The CHMP opinion on the matter (non-pharmacovigilance) referred under Article 31 may be that:

a) the application(s) do(es) (not) satisfy the criteria for authorisation, in this respect;

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

c) the MA(s) should be subject to certain conditions or;

d) MA(s) should be suspended or revoked.

Where the opinion is for the MA(s) to be varied, including changes or added 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 marketing authorisation(s) should be subject to certain conditions for the safe and effective use of the medicinal product(s), 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.

28. How is the CHMP opinion structured?

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

- a cover page in which the adopted opinion is outlined together with the voting outcome of CHMP;
- a listing of all products/applications concerned, including a dedicated list for all identified products authorised nationally, via the mutual recognition/decentralised procedures and their respective marketing authorisation holders (MAHs)/applicants. In case centrally authorised products (CAPs) are involved their respective Annexes A will be attached;
- the scientific grounds and explanation for the CHMP opinion;
- the wording (in English only) to be included in the relevant sections of the summary of product characteristics (SmPC) and/or the labelling or package leaflet (PL), if applicable (only for products authorised nationally including via the mutual recognition/decentralised procedures);
- the revised product information with agreed wording included in the relevant sections of the SmPC and/or the labelling and/or PL, if applicable (only for centrally authorised products);
- the conditions or restrictions imposed to the marketing authorisation(s) for the safe and effective use of medicinal product, if applicable;
- the CHMP members' 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.

29. When is the CHMP opinion published?

A brief outcome of the Committee for Medicinal Products for Human Use (CHMP) opinion will be included in the CHMP meeting highlights that are released on the Friday of the CHMP plenary meeting week, 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 34).

Reference:

Guide to information on human medicines evaluated by EMA

30. Will I receive the CHMP opinion?

The marketing authorisation holder(s)/applicants of products concerned by the scope of the procedure and identified at the start of the procedure will receive the CHMP opinion during the week following the adoption of the CHMP opinion.

31. When and how can I request a re-examination of the CHMP opinion on the Article 31 non-pharmacovigilance referral?

A concerned marketing authorisation holder (MAH)/applicant may, within 15 calendar days of the receipt of the Committee for Medicinal Products for Human Use (CHMP) opinion, notify the Agency in writing of its intention to request a re-examination of the CHMP opinion.

After these 15 calendar days, if the MAH(s) have not requested a re-examination, the CHMP opinion is considered final and is sent to the European Commission (EC).

Re-examination

If within 15 days after the receipt of the CHMP Opinion, a MAH has notified the Agency in writing of its intention to request a re-examination of the CHMP opinion, the Agency will inform the CHMP of the letter of intent received.

The detailed grounds for the re-examination requested should be sent to the Agency within 60 calendar days of receipt of the CHMP opinion. The detailed grounds submitted will determine the scope of the re-examination procedure and may encompass all aspects set out in the CHMP opinion or only certain aspects of it. However, no new data can be presented at this stage of the procedure.

The re-examination procedure will only deal with the aspects of the CHMP opinion identified by the MAH/applicant in the detailed grounds for re-examination. The MAH/applicant may request that the CHMP consults a scientific advisory group (SAG) or ad-hoc expert group during the re-examination procedure. In such a case, this request should be made as early as possible, and should be no later than the submission date of the detailed grounds.

New (co-)rapporteurs will be appointed for the re-examination, and within 60 calendar days of receipt of the detailed grounds for re-examination, the CHMP will conclude its assessment of the detailed grounds and adopt a final opinion.

The CHMP final opinion following re-examination is sent to the EC.

32. When do I have to submit translations?

The marketing authorisation holder(s) (MAHs)/applicants of products authorised nationally (including via the mutual recognition or decentralised procedures) will have to provide translations in all EU languages (including Icelandic and Norwegian, if applicable[3]) of the following annexes to the Committee for Medicinal Products for Human Use (CHMP) opinion:

[3] If authorised in Iceland and Norway

- listing of nationally authorised products (including via the mutual recognition/decentralised procedures) concerned by the procedure;
- wording to be included in the relevant sections of the summary of product characteristics and/or the labelling and/or package leaflet, if applicable.

Only one translation per EU language is required, therefore the MAHs/applicants actively involved in the procedure will be presented with a proposal for worksharing for the translation process. Not all MAHs may be involved in the translation process. MAHs that have not been contacted to participate in the worksharing process will be provided the set of translations at a later stage.

The Agency will contact the MAHs/applicants as early as possible to ensure the smooth running of the worksharing process. The translations will have to be provided to the Member States (MSs) contact points for linguistic check by Day +5 (i.e. 5 days after adoption of the opinion) and copied to the Agency. Member states may send linguistic comments until Day +19. The MAH should send the translations amended accordingly together with the completed QRD form 2 to the Agency by Day +22.

The MAHs/applicants of centrally authorised products (CAPs) involved in the procedure will have to provide the full product information in all EU languages within the same timeframe (i.e. 5 days after adoption of the opinion) and to the MSs contact points for linguistic check and copied to the Agency.

Detailed information on the translation process of the CHMP opinion can be found here.

33. What happens after the final opinion of the CHMP on the Article 31 non-pharmacovigilance referral?

After the final opinion of the Committee for Medicinal Products for Human Use (CHMP), the Agency together with the concerned marketing authorisation holder(s) (MAHs)/applicants 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 decision addressed either to the MAHs/applicants or to MSs and notified to the MAHs/applicants, depending on whether the decision concerns centrally authorised products (CAPs) or nationally authorised products (including via the mutual recognition and decentralised procedures), respectively.

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

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

For NAPs, the CMDh recommendation for implementation of Commission Decisions can be found here.

References:

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

34. Will there be any publication in relation to the Article 31 non-pharmacovigilance referral 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.

Reference:

Guide to information on human medicines evaluated by EMA