REG-89 version 6 Documents Attached to Marketing Authorisation Renewal Applications for medicinal products authorised via national procedure

This guideline supersedes guideline REG-89 version 5 with the effect from July 1 2024.

The Guideline is issued in accordance with the provision of Section 11 of Decree no. 228/2008 Coll.

The Guideline is for recommendation.

Its content is based on legal requirements and EMA and CMDh recommendations which are legally binding.

INTRODUCTION

This instruction aims to define the scope of information and documents submitted to the State Institute for Drug Control ("Institute") along with applications for the renewal of the marketing authorisations for medicinal products authorised via **national procedure** ("renewal application").

The scope of information and documents submitted to the Institute with applications for the renewal of the marketing authorisations for medicinal products authorised via DC/MR procedure follows the guideline CMDh Best Practise Guide on the processing of renewals in the Mutual Recognition and Decentralised Procedures, that is available on the website http://www.hma.eu/95.html.

LEGISLATIVE FRAMEWORK

Under Section 32(2) of Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Associated Acts (Act on Pharmaceuticals), as amended ("Act on Pharmaceuticals"), the marketing authorisation is valid for five years of its effective date. Section 34(1) of the Act on Pharmaceuticals stipulates that the Institute may renew the marketing authorisation after the five years on a review of the benefit/risk ratio. The renewal application should be filed **no later than 9 months prior to the expiry of the marketing authorisation**; therefore, the Institute shall suspend any renewal applications submitted after that date. The validity of a medicinal product's marketing authorisation will thus cease to exist upon the expiry of the marketing authorisation unless an application for the renewal of its validity is submitted within the statutory period of time.

The marketing authorisation holder ("holder") shall provide, along with the application, a consolidated version of the file in respect of **quality, safety and efficacy** including an evaluation of data contained in suspected adverse reaction reports, Periodic Safety Update Report (PSUR) data (if applicable) and any relevant new information affecting the benefit/risk of the product together with a list of all variations introduced since the marketing authorisation was granted. Section 11 of Regulation No. 228/2008 Coll., on Marketing Authorisation of Medicinal Products, as amended ("Marketing Authorisation Regulation"), sets out the **scope of information and documentation attached to the renewal application with the reference to the guideline of the Institute**, which means this document. For renewal applications for medicinal products authorised via national procedure submitted after September 1, 2013 has to be attached the documentation that complies with the requirements, set out herein.

Once the marketing authorisation is renewed one time under the Act on Pharmaceuticals, the marketing authorisation is valid for an unlimited period unless the Institute decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product, to proceed with one additional five-year renewal.

DOCUMENTATION REQUIREMENTS

The holder shall ensure in accordance with Article 23 of Directive 2001/83/EC and Section 33 of Act on Pharmaceuticals that the documentation for each authorised medicinal product be **kept up to date throughout the life cycle of the medicinal product by way of the variation procedures** when new information is found out, and that Summary of Product Characteristics, Package Leaflet and Labelling ("product information") are kept up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available by means of the European medicines web-portal. Along with the renewal application, the holder shall provide a consolidated version of the file relating to the given medicinal product, containing at least the documents listed below. Further documentation should be made available from the holder on request, if considered necessary to complete the benefit/risk assessment. The documentation to be submitted along with the application shall be submitted **electronically, in the eCTD format** in accordance with the requirements stipulated by the effective version of the Institute's Guideline REG-84.

The requirements for individual documents have been adopted from the Marketing Authorisation Regulation and from the guideline CMDh Best Practise Guide on the processing of renewals in the Mutual Recognition and Decentralised Procedures.

More information about the requirements for the submitted dossier:

Module 1: 1.0 Cover letter

1.2 **Completed application form for marketing authorisation renewal** that is available from the website at http://esubmission.ema.europa.eu/eaf/index.html. A single application form may include an application for renewal for one medicinal product (one marketing authorisation number) only. If a revised Summary of Product Characteristics ("SmPC"), labelling and/or package leaflet ("PL") is proposed to take account of issues raised by the expert or formal modification (such as QRD template updates, implementation of warnings as per the Excipient Guideline), the precise present and proposed wording should be specified on the form. Alternatively, such a listing may be provided as a separate document attached to the application form under a tabular format (indicating the current and proposed texts). Any changes not listed will not be considered as part of the renewal application. Any changes not listed will not be considered as part of the renewal application. The renewal application form also incorporates a declaration to be signed that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current Committee for Medicinal Products for Human Use ("CHMP") quality guidelines.

Renewal Application form should be submitted with the following annexes:

- **List of all authorised product presentations** for which renewal is sought, in tabular format
- **Details of contact persons:**
  - Qualified person in the European Economic Area ("EEA") for pharmacovigilance
  - Contact person in the EEA with the overall responsibility for product defects and recalls
  - Contact person for scientific service in the EEA in charge of information about the medicinal product
- **List of EU Member States / Norway / Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date**

- **Chronological list of all post-authorisation submissions** since the granting of the initial marketing authorisation or the last renewal: a list of all approved or pending Type IA & Type IAIN, Type IB and Type II variations, Extensions, Article 61(3) Notifications, and PSURs giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change
- **Chronological list of conditions / post-authorisation commitments** submitted since the granting of the initial marketing authorisation or the last renewal indicating scope, status, date of submission and date when issue resolved (where applicable)
- **A revised list of all remaining conditions** (where applicable)
- **A statement, or when available, a certificate of Good Manufacture Practice ("GMP") compliance**, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application form issued by an EEA competent authority or MRA partner authority. A reference to the Community EudraGMDP database, if available, will suffice
- **For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner**, a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome
- In accordance with Article 46(f) of Directive 2001/83/EC and Section 64(l) of Act on Pharmaceuticals manufacturing authorisation holders (i.e. located in the EEA) are required to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union. The following declarations are required:
  - **A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application form where the active substance is used as a starting material.**
  - **A declaration by the Qualified Person (QP) of the manufacturing authorisation holder(s) listed in the application form as responsible for batch release.**

  These declarations should state that all the active substance manufacturer(s) referred to in the application form operate in compliance with the detailed guidelines on good manufacturing practice for starting materials; manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling as carried out by a distributor. Starting materials manufactured from blood or blood components are excluded from this requirement.

Note: The application form must include a list of all manufacturers of the medicinal product and active substance(s), specifying the activities conducted thereby, consistently with the approved manufacturing chain. Submission of the renewal application shall not replace the obligation to submit applications for variations to marketing authorisation concerning the manufacturing chain.

1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet

The holder shall be obliged to submit an appropriate SmPC, PL and labelling proposal for the medicinal product in the Czech language, with highlighted changes from the latest approved version in the MS Word format. Only changes to the product information based upon an expert's recommendation (see Modules 2.4 and 2.5) or formal amendments modification (such as QRD template updates,

implementation of warnings as per the Excipient Guideline) shall be permissible. Other changes that, in line with Commission Guidelines(on the details of the various categories of variations, on the operation of the procedures laid down in Commission Regulation (EC) No 1234/2008) require the submission of documentation which has to be assessed (Module 4 or 5) shall not be permissible within the scope of the renewal application, as the submission of the renewal application does not replace the obligation to submit applications for variations to marketing authorisation concerning the SmPC, PL, and labelling for the medicinal product.

1.3.2 Graphic proposals of medicinal product packaging (mock-ups)

The submission of the renewal application does not require the submission of mockups. Where mock-ups do form part of the submitted documentation, they shall be subjected to standard assessment. If, during the assessment of the application, it is established that the submission of mock-ups is necessary, the holder may be invited by the Institute to present them.

Within the scope of the renewal authorisation, it is possible to change the design of the mock-ups, introduce multilingual labelling, change the number of languages in which data provided on the labelling are shown, or introduce a foreign-language labelling.

The submission of mock-ups shall be governed by the requirements set forth by the effective version of the Institute's Guideline REG-96.

1.4 Information about the Experts

1.4.1 Information about the Expert – Quality (incl. Signature + CV)

1.4.2 Information about the Expert – Non-Clinical (incl. signature + CV) – only when the Addendum to the Non-Clinical Overview is submitted (Module 2.4)

1.4.3 Information about the Expert – Clinical (incl. Signature + CV)

Module 1.4.3 does not have to be submitted only for products authorised pursuant to Section 28 of Act on Pharmaceuticals (Article 14 of Directive 2001/83/EC).

1.8.2 Risk Management Plan ("RMP")

For medicinal products that have a RMP the holder will be required to submit an update of the RMP with the renewal application in view of reassessing the overall benefit/risk balance of the medicinal product concerned. In case the holder considers that there is no need to change the latest RMP, on the basis of analysis of additional data, given the last RMP updates submitted, a relevant justification in the Cover letter and Module 1.8.2 should be provided. Nevertheless, during the assessment it may be considered that an update of the RMP is necessary and this can be requested by the Institute.

The format and content of the RMP should follow the requirements set out in Commission Implementing Regulation on the performance of pharmacovigilance activities provided for in regulation (EC) No 726/2004 and Directive 2001/83/EC and for which guidance is provided in Module V of the Guidelines on good pharmacovigilance practices ("GVP").

If the product does not have any RMP and the RMP is not required for the product in question, the holder shall state this fact in the cover letter and in Module 1.8.2.

Module 1.8.2 does not have to be submitted only for products registered pursuant to Sections 28 and 30 of the Act on Pharmaceuticals (Articles 14 and 16a of Directive 2001/83/EC).

Module 2: 2.3 Addendum to the Quality Overall Summary

There is no updating of Module 3 quality data at renewal. The holder has an obligation to keep this updated on an on-going basis throughout the life of the product using variation procedures.

The Addendum should be signed and accompanied by the CV of the expert in Module 1.4.1.

The Addendum should include a declaration of compliance with Article 23 of Directive 2001/83/EC and Section 33 of Act on Pharmaceuticals, which obliges holders to take account of technical and scientific progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

The Addendum should include:

- confirmation that all changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CHMP quality guidelines,
- the currently authorised specifications for the active substance and the finished product (with date of last approval),

  Note: The Addendum to the Quality Overall Summary shall contain only approved specifications, as the submission of the renewal application does not replace the obligation to submit applications for variations to marketing authorisation concerning specifications.
- the currently authorised qualitative and quantitative composition in terms of the active substance(s) and the excipient(s).

2.4 Addendum to Non-Clinical Overview

An Addendum to the Non-Clinical Overview is not systematically required as part of the renewal application. In cases where no new non-clinical data have been gathered since the granting of the initial marketing authorisation or the last renewal, this may be stated in the Addendum to the Clinical Overview (Module 2.5).

Where a Non-Clinical Overview Addendum is included it should consist of a critical discussion supporting the benefit/risk re-evaluation for the product considering any new non clinical data accumulated since the granting of the initial marketing authorisation or the last renewal, or any relevant new information in the public domain. The Non-Clinical Overview Addendum should be signed and accompanied by the CV of the non-clinical expert (Module 1.4.2).

The expert should confirm that the authorities have been kept informed of any additional data (e.g. results from new non-clinical studies) significant for the assessment of the benefit/risk balance.

2.5 Addendum to the Clinical Overview

The applicant submits an Addendum to the Clinical Overview. This Addendum should consist of a critical discussion addressing the current benefit/risk balance for the product in each approved indication based on the consolidated version of safety/efficacy data accumulated since the granting of the initial marketing authorisation or the last renewal, taking account of PSUR data, suspected adverse reaction reports, additional pharmacovigilance activities and the effectiveness of risk minimisation measures contained in the RMP. In addition, it should make reference to any relevant new information in the public domain e.g. literature references, clinical trials and clinical experience, new treatments available, which may change the benefit/risk evaluation made at the time of the initial marketing authorisation or the last renewal.

The information shall include both positive and negative results of clinical trials and other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

The Addendum to the Clinical Overview should contain the following information:

- History of pharmacovigilance system inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned) and an analysis of the impact of the findings overall on the benefit/risk balance of the medicinal product.
- Worldwide marketing approval status: overview of number of countries where the product has been approved and marketed worldwide.
- Actions taken for safety reasons during the period covered since the initial marketing authorisation or the last renewal (up to 90 days prior to the renewal submission): description of significant actions related to safety that had a potential influence on the benefit/risk balance of the approved medicinal product (e.g. suspension, withdrawal, temporary halt or premature ending of clinical trial for safety reasons, issue requiring communication to healthcare professionals).
- Significant changes to the SmPC (e.g. safety warnings, contraindication, restriction of indication) during the period covered since the initial marketing authorisation or the last renewal (up to 90 days prior to the renewal submission), or has made changes to the reference safety information that has not yet been agreed for the SmPC. Meaningful differences between the reference safety information and the proposals for SmPC should be stated. A proposed SmPC, PL and labelling should also be provided.
- Estimated exposure: data on cumulative exposure of subjects in clinical trials as well as of patients from marketing exposure. If the holder becomes aware of a pattern of use of the medicinal product considered relevant for the implementation of safety data, a brief description should be provided; such patterns may include in particular, off-label use.
- Data in summary tabulations: summary tabulations of serious adverse events from clinical trials as well as summary tabulations of adverse reactions from post-marketing data sources reported during the period covered since the initial marketing authorisation or the last renewal (until 90 days prior to the renewal submission).
- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies: description of any significant safety findings that had an impact on the conduct of clinical trials or non-interventional studies. It should also address whether milestones from post-authorisation safety studies, post-authorisation efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as conditions and obligations of the marketing authorisation, have been reached in accordance with agreed timeframes.
- Literature: review of important literature references published during the period covered since the initial marketing authorisation or the last renewal (up to 90 days prior to the renewal submission) that had a potential impact on the benefit/risk of the medicinal product.
- Risk evaluation: the holder should summarise any information related to important safety issues, evaluation and characterisation of risks as well as effectiveness of risk minimisation measures for the period covered since

the initial marketing authorisation or the last renewal (up to 90 days prior to the renewal submission).

- Benefit evaluation: the holder should summarise important efficacy and effectiveness information (including information on lack of efficacy) for the period covered since the initial marketing authorisation or the last renewal (up to 90 days prior to the renewal submission).
- Benefit/risk balance: a discussion on the benefit/risk balance for the approved indications should be presented, based on the above information.
- Late breaking information: the holder should summarise the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the Addendum to the Clinical Overview.

Holders are advised to consider the GVP Module VII on PSURs as guidance for the preparation of the above sections of the Addendum to the Clinical Overview.

The above sections can be omitted from the Addendum to the Clinical Overview for products authorised pursuant to Sections 27(1) and (7) of Act on Pharmaceuticals (Articles 10(1) and 10a of Directive 2001/83/EC) and those registered pursuant to Section 30 of Act on Pharmaceuticals (Article 16a of Directive 2001/83/EC), unless there is an obligation to submit PSURs for the product as laid down in a condition to the Marketing Authorisation or it is indicated in the list of European Union Reference Dates (EURD) that PSURs are required for products authorised or registered under these articles and containing the substance or combination of substances concerned.

It should be noted that where PSURs are not required to be submitted, the holder is still obliged to monitor the safety of the product, detect signals and evaluate these and if necessary submit updates through the appropriate regulatory procedure.

The Addendum should be signed and accompanied by the CV of the expert (submitted in Module 1.4.3). The clinical expert should have the necessary technical or professional qualifications and may, but not necessarily, be the same as qualified person responsible for pharmacovigilance.

In any event a clinical expert statement will be required and the Clinical Expert should:

- Confirm that no new clinical data (or pre-clinical data in the absence of an Addendum to the Non-Clinical Overview) are available which changes or results in a new benefit/risk evaluation. Where there are new pre-clinical data, the holder should submit a non-clinical expert report as appropriate.
- Confirm that the product can be safely renewed at the end of a 5-year period for an unlimited period or any action recommended or initiated, for example, recommendation for further review in 5 years-time should be specified and justified. The expert should ensure that the updated benefit/risk evaluation has been addressed adequately, taking account of the consolidated version of the file and all relevant new information.
- Confirm that the authorities have been kept informed of any additional data significant for the assessment of the benefit/risk balance of the product concerned.
- Confirm that the product information is up to date with current scientific knowledge including the conclusions of assessments and recommendations made publicly available on the European medicines web-portal.

Module 2.5 does not have to be submitted only for products registered pursuant to Section 28 of the Act on Pharmaceuticals (Article 14 of Directive 2001/83/EC).

REQUIREMENTS FOR SUBMISSION OF DOCUMENTATION

1) The aforementioned documentation should be submitted **in electronic form in the eCTD format according to the requirements set out in the Guideline REG-84 in valid version**.
2) The renewal application may be submitted only by a person authorised/appointed to do so. The requirements for the submission of Powers of Attorney/authorisations, including specimen Powers of Attorney are available from the website at: http://www.sukl.eu/sukl/example-letter-of-authorisation.