HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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Guide to
Renewal of Marketing Authorisations – Human Medicines

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

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1 APPLICATION FORMS

An application for renewal of a marketing authorisation must be made using the following form:

- EU form application for renewal of a marketing authorisation, available from the website of the EU Commission or from the HPRA website.

2 SUBMISSION OF DOCUMENTATION

Applications must be submitted at least nine months before the expiry of the current authorisation, in accordance with article 24 of Directive 2001/83/EC as amended by Directive 2010/84/EC.

Each application, whether authorised nationally or through mutual recognition, must be accompanied by the EU application form in order for it to be validated. A covering letter should also be included.

Applicants should ensure the accuracy of all documentation submitted, including the information provided in the application form.

Applications which do not include the required documents, including an addendum to the clinical overview in module 2 and label and leaflet colour mock-ups, will not be validated.

Please see the HPRA 'Guide to Electronic Submissions – Human Medicines' for details on sending the application to the HPRA.

3 EU FORM DATA REQUIREMENTS

The guidance given in this section is additional to that given in the EU Commission's guideline on the processing of renewals in the mutual recognition and decentralised procedures, which is of relevance to all renewal applications including those not authorised through the mutual recognition procedure.

3.1 Summary of Product Characteristics (SmPC)

The latest version of the SmPC approved by the HPRA should be submitted with the renewal application. Proposals to change the SmPC are generally not acceptable at renewal, however the following exceptions apply:

- changes arising from the review of the addendum to the clinical overview, which are considered to relate to significant safety issues

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- editorial changes proposed in order to comply with European guidelines (e.g. guideline on Summary of Product Characteristics) which do not alter the substance of the previously approved SmPC

It is strongly recommended that MA holders amend the SmPC to take account of the addendum to the clinical overview or to comply with the SmPC guideline **before** submitting the renewal application, in order to expedite the assessment. Where changes are proposed, an annotated version of the SmPC should be submitted, with all proposed changes highlighted.

Information on how to prepare and review an SmPC is available from the websites of the European Commission (EC), the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA). The EC Guideline on Summary of Product Characteristics (SmPC) and the CMDh QRD annotated template for MR/DCP are particularly useful. Use of these resources is encouraged as it significantly reduces the amount of re-formatting required to convert submitted files into standard HPRA documents.

Deleted: A standard SmPC template is available on the HPRA website, as part of a template for the marketing authorisation. The template includes standard statements from the EMA's quality review of document's product information template. Use of this template

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3.2 Labels and package leaflet

Labels and leaflets as approved by the HPRA should be submitted. Full colour mock-ups of the actual sales presentation should be submitted unless the product is not marketed, in which case black and white text suffice.

It is strongly recommended that labels and leaflets are updated in line with current EU requirements. Any changes should be clearly highlighted on the submitted label and package leaflet mock-ups.

3.3 Addendum to the clinical overview

An addendum to the clinical overview must be submitted with all renewal applications. The addendum must consist of a critical discussion addressing the current benefit/risk balance for the product, on the basis of the consolidated safety and efficacy data accumulated since the granting of the initial MA or the last renewal, taking into account suspected adverse reaction reports, additional pharmacovigilance activities and the effectiveness of risk minimisation measures contained in the risk management plan (RMP). It must also make reference to any relevant new information in the public domain, such as literature references, clinical trials and new treatments available, which may change the benefit/risk evaluation made at the time of the original authorisation or last renewal. The addendum must be signed by and accompanied by the CV of the clinical expert. A clear conclusive statement is required from the clinical expert that the product can safely be reviewed at the end of the 5 year period for an unlimited period or any action recommended such as a further renewal in 5 years time. Refer to the CMDh BPG on renewals on the CMDh website. Marketing authorisation holders

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(MAHs) are also advised to consider the GVP Module VII on PSURs as guidance for the preparation of the above sections of the clinical overview.

3.4 Risk management plan

For products with an existing RMP, the MAH must submit either:

a an update of the approved RMP based on reassessment of the overall benefit/risk balance of the product and analysis of any additional data since the last approved RMP

or

b a declaration justifying why no amendments are required to the last approved RMP along with a confirmation that the current approved RMP remains unchanged and applicable; this should be provided in the addendum to the clinical overview (module 2.5)

A new RMP may also be submitted as part of the renewal application where relevant.

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 of the European Parliament and of the Council. Further guidance is provided in Module V of the Guideline on Good Pharmacovigilance Practices.

For products without an existing RMP, this should be indicated in module 1.8.2.

Reference to submission or non-submission (with brief justification in the case non-submission) of an RMP should be included in the covering letter to the HPRA.

3.5 Manufacturers

For sites within the EEA, current manufacturing authorisations or certificates of GMP compliance should be provided for all sites of manufacture, assembly, sterilisation and batch release of the finished product. Manufacturing authorisations or GMP certificates should show that the manufacturer is currently authorised for the manufacturing operations specified in the marketing authorisation.
For sites outside the EEA, documentary evidence issued by an EEA competent authority or MRA partner authority indicating the date, inspection team and outcome of the most recent inspection at the site is required for all sites of manufacture, assembly and sterilisation.

Declarations are required in relation to the GMP status of the active substance(s), for more details please refer to the EU renewal application form.

PA holders are asked to ensure that the manufacturers of the active substance and finished product listed in the form are those approved by the HPRA. Any change in manufacturers must be done by variation before submission of the renewal.

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3.6 Quality overview

The quality overview must be signed and accompanied by the CV of the expert. It should include a declaration of compliance with Article 23 of Directive 2001/83/EC, as amended, which obliges MA holders to '...take account of technical and scientific progress and introduce any changes...'. The statement should confirm that all changes relating to the quality of the product have been made following applications for variations. The statement should also include the currently authorised specifications for the active substance and the finished product and the qualitative and quantitative composition in terms of the active substance(s) and the excipient(s). MA holders are asked to check that the composition, specifications and the references to test methods submitted with the application are those approved by the HPRA. Any revision of the specifications to bring them into line with current requirements, including pharmacopoeial standards, must be done by variation before submission of the renewal.

In addition the statement should confirm that the product conforms to current CHMP quality guidelines where relevant e.g. Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95) and Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01). Updated TSE certificates must be submitted by variation using the appropriate category in line with the 'Guideline on Dossier Requirements for Type 1A and Type 1B notifications.'

If the MA holder is submitting updated stability data to fulfil commitments provided during previous regulatory activities, reference to the documentation should be made in the cover letter for the renewal application. When submitting updated stability studies, the MA holder should confirm that the formulation, packaging materials and analytical methods used are those previously approved, and include a conclusion based on the results of the stability studies.

4 GUIDANCE FOR SPECIFIC PRODUCT TYPES

4.1 Products within the mutual recognition procedure

For products for which Ireland is the Reference Member State, MA holders are asked to fix the common renewal date no later than the date of expiry of the Irish MA. Applications for an MR renewal procedure at a date beyond the expiry of the Irish MA will generally not be accepted.

For products for which Ireland is a Concerned Member State and where the Irish MA expires before the MR renewal application is due or before the common MR renewal date, a national

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renewal application must be made so that an MA can be issued to cover the period between expiry of the authorisation and the common MR renewal date.

4.2 Parenteral products

Companies holding multiple MAs for a range of parenteral products that differ only in container volume may take the opportunity to merge the MAs at the renewal stage if the products meet the criteria for merging which are detailed in the HPRA guidance on combining parenteral product containers on one product authorisation, available from the HPRA website. If it is proposed to merge MAs, this should be stated in the covering letter submitted with the renewal application.

5 GENERAL

5.1 Changes to MAs

Apart from changes to the SmPC, labels and leaflets as outlined above, an application for a change in the conditions of the authorisation may not be made as part of the renewal application. Any such change will not be assessed as part of the renewal procedure and will only be approved following a subsequent application through the variations procedure.

5.2 Common renewal dates

Requests to bring forward a renewal date for one or more products in order to synchronise the renewal dates for a range of product strengths are generally facilitated. Any such proposal should be agreed with the HPRA in advance of the proposed date and requests should be directed to the Receipts and Validation section in the first instance.

5.3 Renewal application procedure

During the renewal procedure, MA holders will be sent a draft MA schedule for comment. Responses should include any corrections to the draft schedule annotated on the copy which is sent to the applicant and signed and dated colour mock-ups of the labels and leaflet which have been amended in line with comments from the assessors. Failure to respond or the submission of an incomplete response will result in the MA being considered withdrawn and the files closed. Any corrections to the schedule required after it has been issued must be applied for using the variation procedure.

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