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NOTICE TO APPLICANTS
VETERINARY MEDICINAL PRODUCTS

A GUIDELINE ON THE PROCESSING OF RENEWALS IN THE CENTRALISED PROCEDURE June 2002

This guideline will be included in the Rules governing medicinal products in the European Community Volume 6C Regulatory guidelines. The application form and guidance note are common to the renewal procedure for human medicinal products and are likewise included in Volume 6C.

GUIDELINE ON THE PROCESSING OF RENEWALS IN THE CENTRALISED PROCEDURE

1. Introduction

This paper considers issues associated with the processing of renewals in the centralised procedure, with an aim of giving procedural guidance to marketing authorisation holders (MAHs).

It has been developed following consultation of the CVMP and the European Commission.

2. Legal Framework

In accordance with Article 28 of Directive 2001/82/EC and Article 35 of Council Regulation (EEC) No. 2309/93 as amended, a marketing authorisation is valid for five years and renewable for five yearly periods upon application by the marketing authorisation holder. The renewal dossier should contain in particular details of the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product. Directive 2001/82/EC requires the submission of a periodic safety update.

Certain changes to the marketing authorisation particulars may be made at renewal, and these changes shall not trigger a variation procedure. Further details of permitted changes are given in Section 3.5 Assessment Process. However, none of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.

3. Principles of submission and evaluation

3.1. Date for renewal

Marketing authorisation holders must apply at least three months in advance of the expiry date, i.e. the 5 year anniversary of the Commission Decision granting the marketing authorisation, for the application to be valid under Article 28 of Directive 2001/82/EC and Article 35 of Council Regulation (EEC) No. 2309/93, as amended. Flexibility will be maintained as to the basis of the renewal date and will take account of the International Birth Date, and the maintenance of synchronisation of PSURs. The marketing authorisation holder should agree in advance the submission date of the renewal application with the EMEA and the Rapporteur/Co-Rapporteur.

3.2 Date for submission

The renewal submission is required no later than 3 months before the expiry date. However to allow the marketing authorisation holder to submit PSUR data from the last data lock point with the renewal application, and to process the application within the timetable agreed at CVMP level, it is strongly recommended that the renewal submission is made **4 months** ahead of the renewal date.

Reference should be made to the new Volume 9 of the Rules Governing Medicinal Products in the European Union on Pharmacovigilance (Notice to Marketing Authorisation Holders). In accordance with such Notice to Marketing Authorisation Holders the following principles should be taken into account:

- Data lock points may be set according to the EU Birth Date of a medicinal product or its International Birth Date and PSURs should be submitted with the following frequency:
    - immediately upon request
    - 6 monthly for the first 2 years after authorisation

- annually for the subsequent 2 years
- at the first renewal
- thereafter 5 yearly at renewal

- The PSUR should be submitted within 60 days of the last data lock point. Marketing authorisation holders should lock their data no more than 60 days before submitting the application for renewal. For the first renewal, a 6-months PSUR (i.e. data lock-point of 4 ½ years) is to be submitted.
- The marketing authorisation holder should submit the renewal application at least 3 months before the expiry of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate co-ordination with the regular cycle of the PSUR.

  (Note - the 4-month submission date maintains this principle).

The aim will be to grant the renewal before or on the due date to ensure synchronisation is maintained.

If the renewal takes longer to resolve, the product may remain on the market whilst the renewal application is pending. When issued, the renewal decision will take the expiry date of the preceding marketing authorisation so that the renewed authorisation will expire at the end of the 5-year period from the date of the previous expiry. This is essential for the synchronisation of the PSURs (see Annex 1 for definitions).

3.3 Timetable

In order to allow sufficient time for the scientific evaluation of the data submitted and the transformation of the CVMP opinion into a Commission Decision, and acknowledging that the overall process should be finalised in 4 months, the timetable (of max. 90 days) for the scientific evaluation by the CVMP is as follows (see also Annex 2):

- Start:Following validation after submission on recommended date.
- Rapporteur's Assessment Report sent to Co-Rapporteur: day 40
- Joint Rapporteur/Co-Rapporteur Assessment Report: day 50.

  (Circulate to CVMP and MAH, highlighting major issues if any)
- First discussion at CVMP: day 60*.
  - If no outstanding issues: adoption of opinion
  - If outstanding issues: adoption of list of outstanding issues + decision on possible oral explanation by MAH
- MAH provides answers to list of outstanding issues to (Co-)Rapporteur, CVMP and EMEA: day 70.
- Revised Assessment Report from Rapporteur/Co-Rapporteur: day 80

  (Circulate to CVMP and MAH)
- Adoption of CVMP Opinion/oral explanation by MAH: day 90.

  *: At day 60 a first discussion on the joint Assessment Report will take place at the CVMP.

If any remaining outstanding issues are identified, including serious public or animal health or environmental concerns, which may lead to a negative benefit/risk ratio and a possible non-

renewal or to major changes to the marketing authorisation, a list of such issues will be adopted and sent to the MAH to be addressed in writing and/or at an oral explanation.

A limited extension of the timeframe is possible allowing the marketing authorisation holder to respond to the list of outstanding issues and the CVMP to assess the additional data submitted.

The timetable will be adopted by the CVMP at the start of the procedure following a positive validation of the renewal application.

3.4 Documents to submit

A list of documents to submit is given in Annex 3. Details on the number of copies of the dossier to be submitted are given in Chapter 7 of the Notice To Applicants (Volume 6A) at http://pharmacos.eudra.org/F2/eudralex/vol-6/home.htm

The European renewal application form should be completed.
The form is available in the Notice To Applicants (Volume 6C) at
http://eudradev.entr.cec.eu.int/F2/eudralex/vol-6/home.htm#6c (i.e. the same form as for human medicinal products).

The marketing authorisation holder should complete one renewal application form for the Centrally Authorised Medicinal Product, appending a list of all authorised strengths, pharmaceutical forms and presentations of the product concerned (= 1 application per core EU Number). If a revised SPC is proposed to take account of issues raised by the expert, the precise present and proposed wording should be specified on the form. In general, proposed amendments to the SPC should be brought to the attention of the EMEA before submission, preferably through a pre-renewal submission meeting. 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 CVMP quality guidelines, where relevant.

PSUR and Safety Expert Statement:

For the first renewal, a 6-months PSUR (i.e. data lock-point of 4 ½ years) is to be submitted.

For subsequent renewals, a 5-year PSUR is required unless the PSUR submission cycle had been restarted. Where for the second and/or subsequent renewals the MAH does not submit a single 5-year PSUR but PSURs based on multiples of 6 months[1], an additional bridging PSUR summary report is required covering the 5-year period. The PSUR bridging report should not repeat the information already included in the PSURs. If there is a need the MAH can cross-refer to relevant sections of the appropriate PSURs. Such PSUR bridging report should consist of, but not necessarily be restricted to:

- a listing of all safety concerns (incl. any discussion where necessary) which emerged during the 5 years and which have been resolved or are still outstanding, regardless of their being listed/expected and seriousness;
- an exposure estimation of the 5 years period expressed in number of animals treated;
- information on studies or other information on (possible) extensions of indications or animal populations, if applicable.

[1] This might occur for MAHs with worldwide authorisations

A human safety expert statement must be provided to include a discussion of user and consumer safety, which reviews the available information that has come to light in the reporting period.

Clinical Expert Statement. The marketing authorisation holder submits an expert statement to accompany the renewal application which addresses the current risk/benefit for the product on the basis of PSUR data and 5-year compiled data (4½ years for the first renewal) and makes 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 outcome of the risk/benefit evaluation at the time of the original authorisation or last renewal.

It is recognised that the PSUR required to be included in the renewal submission should already contain a summary addressing a risk/benefit evaluation conforming to VICH guideline 29 ("Pharmacovigilance of veterinary medicinal products: management of Periodic Safety Update Reports") which is currently in consultation. This summary could be considered as an addendum to the clinical expert statement.

The expert statement must be signed and accompanied by a CV of the expert. The clinical expert should have a veterinary qualification and may, but should not necessarily, be the same qualified person responsible for pharmacovigilance.

In any event, a clear statement is required from the clinical expert that the product can be safely renewed at the end of a 5-year period for a further term, or any action recommended or initiated should be specified and justified. The intention is that the clinical expert takes responsibility in the renewal application for the continued availability of the product on the market. The expert should ensure that the updated risk/benefit evaluation has been addressed adequately, taking account of all relevant new information, either by endorsement of the statement within the PSUR or by appropriate supplementation within the expert statement.

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

Updating of Quality – Quality Expert Statement. There is no updating of Part II quality data at renewal. The marketing authorisation holder has an obligation to keep this updated on an on-going basis throughout the life of the product using the variation procedure.

The quality expert statement should include a declaration of compliance with Article 27(1) (Directive 2001/82/EC) which obliges marketing authorisation 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 and that the product conforms to current CVMP quality guidelines. 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). The expert statement must be signed and accompanied by a CV of the expert.

The marketing authorisation holder will continue to monitor the stability of the product in accordance with agreed stability protocols but needs only to inform competent authorities should a problem arise together with a recommended course of action. This reflects the principles of the Type I variation dossier requirement guideline. A copy of an updated statement of compliance with Good Manufacturing Practice from the competent authority, which is not older than 3 years, should be submitted with the renewal application as well as a

list of most recent GMP inspections carried out at all manufacturing sites of the finished product indicating the date, inspection team and outcome.

3.5 Assessment process

The assessment will focus on a safety evaluation, making use of the PSUR data and any relevant new information affecting the risk/benefit for the product, thus allowing for a re-evaluation of the risk/benefit of the product. A full re-evaluation of the whole dossier normally should not take place. Serious public or animal health or environmental concerns should be addressed as part of the renewal process and the product will not be renewed if serious public or animal health or environmental issues remain at the end of the procedure (see also section 3.6.2).

Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms and changes are necessary to the SPC arising from the PSUR evaluation, the marketing authorisation holder may submit additional information and/or change the product information as part of the renewal process to address the concerns raised. Such changes will not initiate a separate variation procedure.

Other issues arising from assessment and changes due to the revision of the SPC guideline, or EMEA/QRD Product Information Templates should be considered within the renewal process. Proposed changes to the SPC will be indicated on the renewal application form.

Major changes to the product, such as the introduction of new indications or an extension of shelf life, may not be modified through the renewal procedure and have to be assessed through a variation procedure.

None of the SPC changes introduced at renewal should substitute for the marketing authorisation holder obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.

In very exceptional cases, if as part of the renewal assessment, new studies are required, but these are not of such importance as to delay issue of the renewal, then these may be considered as on-going post-authorisation commitments (Follow-Up measures) after the issue of the renewal. The marketing authorisation holder will be required to provide written assurance that it will undertake the on-going commitments *(*(Follow-Up measures) within an agreed time frame. If the results of new studies lead to changes in the SPC, these will be processed through a separate Type II variation procedure (see also section 3.6.2).

As part of the renewal process, the EMEA, in collaboration with the Member States, will check that the SPC, labelling and package insert conform to Title V of Directive 2001/82/EC requirements.

3.6. The Committee's opinion

The CVMP will adopt an opinion on the renewal in the light of the final recommendation of the Rapporteur and Co-Rapporteur. The draft opinion is prepared by the EMEA and then adopted by the CVMP.

The CVMP opinion, which may be favourable or unfavourable, is, wherever possible, reached by scientific consensus. If such consensus cannot be reached, the Opinion shall be adopted by a majority of the members. When divergent positions have been expressed, they will be referenced in the CVMP Opinion. Members expressing such divergent positions shall state clearly the grounds on which they are based. The divergent positions will be appended to the Opinion.

Where the Opinion is adopted by a majority vote, the number of votes shall be clearly mentioned in the Opinion. In the absence of a majority position the CVMP Opinion is deemed to be negative.

The position of the Norwegian and Icelandic CVMP members, who do not take part in the CVMP vote as such, is nevertheless recorded in the opinion.

The Rapporteur, in co-ordination with the Co-Rapporteur and the project manager, taking account of the full scientific debate within the CVMP and the conclusions reached, prepares the final renewal assessment report, which, once adopted by the CVMP, becomes the CVMP renewal assessment report and is appended to the CVMP opinion.

3.6.1 Favourable opinion

In the event of an opinion in favour of renewal of the authorisation, the following documents will be annexed and/or appended to the opinion.

- A draft Summary of Product Characteristics as referred to in Article 14 of Directive 2001/82/EC if revised during the renewal assessment;
- Manufacturing and/or importing conditions and conditions of the marketing authorisation, if revised during the renewal assessment;
- A classification for the supply of the medicinal product, if revised during the renewal assessment;
- A draft Label and Package insert presented in accordance with Title V of Directive 2001/82/EC, if revised during the renewal assessment;
- The CVMP renewal assessment report;
- Where relevant, divergent positions of Committee Members with signatures and with their grounds for not supporting the opinion

  Any follow-up measures agreed upon by the CVMP will be included in the renewal assessment report and referenced in a letter of undertaking signed by the Marketing Authorisation Holder which will be annexed to the assessment report (see also 3.6.1.2).

3.6.1.1 Opinion on products authorised under exceptional circumstances

The fifth annual re-assessment of medicinal products authorised under exceptional circumstances will take place at the renewal of the product concerned.

For such medicinal products authorised under exceptional circumstances, in accordance with Article 35(2) of Council Regulation (EEC) No. 2309/93, the CVMP will have to consider whether there remain grounds for the marketing authorisation to be kept under exceptional circumstances. If no such grounds remain, a recommendation will be made to renew the marketing authorisation under normal circumstances.

3.6.1.2 Post-Authorisation commitments

Specific obligations

When a renewal Opinion is granted, stating that there remain grounds for the marketing authorisation to be renewed under exceptional circumstances, the marketing authorisation holder is obliged to submit the requested data to the Rapporteur, Co- Rapporteur, CVMP Members and the EMEA, in the agreed timeframe after the renewal. These "specific obligations" to provide such data, are set out in Annex II of the Opinion and are detailed in the Letter of Undertaking of the marketing authorisation holder as adopted at the time of the Opinion. The specific obligations are to be reviewed at the intervals indicated and at the longest annually. The annual review includes a re-assessment of the benefit/risk profile.

A copy of the documentation relating to specific obligations should be sent by the marketing authorisation holder to the Chairman of the CVMP, all CVMP members and EMEA. Such documentation should be reviewed in accordance with the agreed timetable.

Follow-up measures

For all opinions of the CVMP (whether or not under the exceptional circumstances of Article 35(2) of the Regulation), it might be necessary to establish follow-up measures. Unless otherwise requested by CVMP members, the data on the fulfilment of follow-up measures should be sent by the marketing authorisation holder to the Rapporteur and the EMEA. The data should be reviewed in accordance with the agreed timetable. Marketing authorisation holders will be informed of the outcome of CVMP discussions by the EMEA.

Resulting variation applications

Marketing authorisation holders are encouraged to submit any variation application resulting from the fulfilment of follow-up measures and /or specific obligations at the same time as the fulfilment of the follow-up measures/ specific obligations to minimise the processing and review time.

3.6.2. Unfavourable opinion

The CVMP will adopt a negative opinion recommending not to renew the marketing authorisation if there are serious public or animal health issues raised. The criteria specified in Article 83 of Directive 2001/82/EC regarding the suspension or revocation of authorisation to market medicinal products form the basis for the refusal to renew the marketing authorisation.

These criteria include where the product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results cannot be obtained with the medicinal product. Additionally, non-renewal may be considered where the particulars supporting the application for renewal are incorrect or have not been updated, or when the controls on the manufacturing process or on the finished product have not been carried out, or when commitments have not been fulfilled.

Additionally, non-renewal will be considered if the marketing authorisation holder fails to respond to the issues raised during assessment within the timescale given and where no adequate justification or explanation is given.

The following documents will be annexed and/or appended to the opinion:

- the appended CVMP assessment report stating the reasons for its negative conclusions.
- where appropriate, divergent positions of Committee Members with their grounds.

3.7 Follow-up to the CVMP opinion

3.7.1 Translation and transmission of the CVMP opinion

If amendments to the proposed product information are required following the adoption of the CVMP opinion, the marketing authorisation holder will provide the EMEA and all CVMP members with the relevant amended translations of the SPC, labelling and package insert within 5 days after the CVMP opinion.

During the evaluation procedure, a review of the quality of the translations will be carried out by the EMEA in co-operation with the Member States. The Norwegian and Icelandic translations will be checked by the Norwegian and Icelandic authorities in co-operation with the EMEA.

If within 15 days of receipt of the opinion, the marketing authorisation holder does not inform the EMEA of any intention to appeal, the EMEA will then forward the opinion (and the required annexes), to the Commission, the Member States, Norway and Iceland and the marketing authorisation holder together with the CVMP assessment report. The opinion and its annexes is sent either by electronic mail or by courier (if electronic mail is not available).

The Decision-Making Process of the Commission starts once the opinion with annexes in all official EU languages, as appropriate, has been received. The Norwegian and Icelandic Authorities will issue corresponding national authorisations subsequent to the Commission Decision.

Where the CVMP adopted a negative opinion and the marketing authorisation holder notified the EMEA/CPMP of their intention of appeal, the EMEA will inform the Commission about such negative opinion and appeal. The final CVMP opinion will be forwarded to the Commission upon finalisation of the appeal procedure (see 3.7.3).

3.7.2 Mock-ups and specimens

Where the package insert and outer and inner labelling have been amended as a result of the renewal procedure, updated mock-ups should be provided to the EMEA shortly after adoption of the CVMP opinion.

For Norway and Iceland, new mock-ups for all product presentations covered by the renewal application should be provided to the Norwegian and Icelandic authorities (with a copy of the cover letter to the EMEA) in all cases. One set of specimens, approved by the Norwegian and Icelandic authorities should be sent by the MAH to the EMEA for information.

3.7.3. Appeal

The marketing authorisation holder may notify the EMEA/CVMP of their intention to appeal within 15 days of receipt of the opinion (after which if he does not appeal, he shall be deemed to have agreed with the opinion and it becomes a final opinion).

The grounds for appeal must be forwarded to the EMEA within 60 days of receipt of the opinion. If the marketing authorisation holder wishes to appear before the CVMP for an oral explanation, the request should also be sent at this stage. The CVMP may decide to appoint a new Rapporteur and Co-Rapporteur, for whom MAHs can express their preference, to co-ordinate the appeal procedure, accompanied, if necessary, by additional experts. Within 60 days from the receipt of the grounds for appeal, the CVMP will consider whether its opinion is to be revised. If considered necessary, an oral explanation can be held within this 60-day timeframe.

Once the CVMP issues a final opinion, it is forwarded (with the required annexes), to the Commission, the Member States, Norway and Iceland and the marketing authorisation holder stating the reasons for its conclusion.

3.7.4 European Public Assessment Report (EPAR)

The EMEA will prepare an update of the EPAR, reflecting the renewal assessment and CVMP opinion. The draft updated EPAR will be circulated to members of the CVMP at a subsequent meeting. Once the CVMP has agreed on the updated text and after the Commission Decision on the renewal has been made, the updated EPAR shall be made available from the date of the Commission's Decision to renew the marketing authorisation.

3.7.5 Negative decision

Following a Commission Decision on the refusal to renew the marketing authorisation, which, in accordance with Article 34.2 of the Regulation, constitutes a prohibition to maintain on the market the medicinal product concerned throughout the Community, the EMEA shall, upon request, inform any person concerned of the final Decision, in accordance with Article 32.4 of the Regulation.

ANNEX 1

DEFINITIONS

(REFERENCE VOLUME 9 - PHARMACOVIGILANCE, THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION)

Data Lock-Point (cut off date)

The date designated as the cut-off date to be included in a periodic safety update report (PSUR).

International Birth Date (IBD)

The date of the first marketing authorisation for a medicinal product granted to the marketing authorisation holder in any country in the world.

EU Birth Date (EBD)

The date of the first marketing authorisation for a medicinal product granted in the European Union (EU) to the marketing authorisation holder:

- For medicinal products authorised through the centralised procedure, the EU Birth Date is the date of the marketing authorisation granted by the European Commission (Commission Decision Date). (However, some flexibility may be use in order to harmonise periodic safety updates internationally. Thus the month for data lock may be +/- six months within the EC birth date, provided that the first periodic safety update is submitted not later than 6 months after the EC birth date.
- For medicinal products authorised through the mutual recognition procedure, the EU Birth Date is the date of the marketing authorisation granted by the reference Member State.
- For products authorised nationally, the marketing authorisation holder may propose an EU Birth Date, which can be applied to reporting requirements across the Member States.

ANNEX 2

RENEWAL TIMETABLE (CVMP)

Day 1	Start of procedure
Day 40	Rapporteur's Assessment Report sent to Co-Rapporteur
Day 50	Joint Rapporteur / Co-Rapporteur Assessment report circulated to EMEA, CVMP members and MAH.
Day 60	First discussion at CVMP. - Possible adoption of opinion. - In case of outstanding issues: adoption of list of outstanding issues + decision on possible oral explanation by MAH
Day 70	MAH provides answers to list of outstanding issues to Rapporteur, Co-Rapporteur, CVMP and EMEA
Day 80	Revised Rapporteur / Co-Rapporteur Assessment Report circulated to EMEA, CVMP members and MAH.
Day 90	Adoption of CVMP opinion Possible oral explanation by MAH

The renewal application should be submitted at the latest 5 working days before the start of the procedure (i.e.on the recommended submission date) to the EMEA, Rapporteur / Co-Rapporteur and CVMP members. The application is validated by the EMEA within 5 working days following submission. Once validated, the marketing authorisation holder, the Rapporteur and Co-Rapporteur and other CVMP members are informed, the timetable is adopted and the clock starts accordingly.

ANNEX 3

DOCUMENTS TO SUBMIT

The marketing authorisation holder submits a renewal application to the EMEA and all CVMP members[2] comprising the European renewal application form with the following annexes:

1.1 List of all authorised product presentations in tabular format (following the template for Annex A to CVMP Opinions)

1.2 Details on contact persons:

- qualified person in the EEA for Pharmacovigilance
- contact person in the EEA with overall responsibility for product defects and recalls
- contact person for scientific service in the EEA in charge of information about the medicinal product

1.3 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

1.4. Chronological list of Follow-up measures and Specific Obligations submitted since grant of marketing authorisation or last renewal indicating scope, status, date of submission and date when issue has been resolved

1.5. Revised list of all remaining Follow-up measures and Specific Obligations and signed letter of commitment (where applicable)

1.6. Proof of payment of fee

2. Proposed texts for SPC, outer and inner labelling and package insert in 13 languages (EU, Norway and Iceland), together with 1 example of a currently marketed printed package insert. For submission to CVMP members, only the relevant language version(s) and printed package insert are to be provided in addition to the English product information

3.1 Quality expert statement including:

3.1.1 Currently authorised specifications for the active substance and the finished product (with date of latest approval + procedure number).

3.1.2 Qualitative and quantitative composition in terms of the active substance(s) and the excipient(s) (with date of latest approval + procedure number)

3.2 Statement of GMP compliance (from competent authority, not older than three years)

3.3 List of most recent GMP inspections carried out at all manufacturing sites of the finished product indicating the date, inspection team and outcome

4.1 Clinical expert statement.

4.2 Required Periodic Safety Update Report (i.e. data lock point of 4½ years for first renewal and 5-year PSUR for subsequent renewals) and Safety expert statement.

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[2] number of copies and language requirements: see Chapter 7 of the Notice to Applicants (Volume 6A)