Q&A – Generic Applications

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Submission of a description of Pharmacovigilance System and EU Risk Management Plans for Generic and Hybrid Applications

1. Is submission of a summary of a pharmacovigilance system required for generic or hybrid applications?

The requirements for submission of the summary of a pharmacovigilance system are the same as for any marketing authorisation application, independent of the legal basis of the application. These requirements are described in Directive 2010/84/EU amending Directive 2001/83/EC.

For further guidance consult the Guideline on good vigilance practices (GVP) Module II.

2. Should an EU Risk Management Plan be submitted as part of an application for a generic product?

The answer is indicated in the EMA / HMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation, no.3.1. For further guidance consult the Guideline on good vigilance practices (GVP) Module V.

3. Are there special requirements regarding the submission of EU Risk Management Plans for hybrid applications?

The requirements for submission of EU Risk Management Plans for hybrid applications are the same as for any marketing authorisation application, independent of the legal basis of the application. These requirements are described in Directive 2010/84/EU amending Directive 2001/83/EC.

Possibility to refer to clinical studies performed by a company different from the company holding the initial Marketing Authorisation

4. Is it possible in an application for marketing authorisation based on an abridged dossier to refer both to the complete dossier of a reference product and to clinical studies contained in a hybrid dossier according to Article 10(3) of Directive 2001/83/EC, from a Marketing Authorisation Holder (MAH) different from the MAH of the reference product?

The EC has confirmed the admissibility of an application for marketing authorisation based on an abridged dossier, which refers both to the complete dossier of a reference product and to clinical studies contained in a hybrid dossier, authorised according to Article 10(3) of Directive 2001/83/EC.

The non-admissibility of such an application, referring to new clinical studies developed for a medicinal product authorised as a hybrid would entail an indefinite protection of these studies, which is not intended in the Community legislation.

In the context of this Q&A and in line with the information published at the NtA, the clinical studies that may be referred to should be those that resulted in new clinical data and with predefined clinical endpoints justifying differences of clinical particulars of a MA (e.g. new indication, strength, route of administration, pharmaceutical form).
Applicants are advised to discuss the dossier requirements in such situations with the Reference Member State.

Applicants should indicate in the application form only one reference medicinal product that has to be either approved under Article 8(3) or 10a and make reference in the cover letter to the studies in the Article 10(3) application. The product used in the bioequivalence study should not be included in section 1.4.3 of the application form. The applicant should make reference in the cover letter to the studies in the Article 10(3) application.

Legal basis for generic applications where the reference medicinal product in the CMS(s) has fewer indication(s) than in the RMS

5. What should be the legal basis of a generic application, i.e. Article 10(1) vs. 10(3) of Directive 2001/83/EC in the situation where the reference medicinal product in a Concerned Member State (CMS) has fewer therapeutic indications than in the Reference Member State (RMS) and as such not all of the therapeutic indications applied for by the generic product have been granted to the reference medicinal product in the CMS(s)?

It has been agreed by the CMDh and confirmed by the EC that in the situations where the summary of product characteristics for the reference medicinal product is not harmonised between the RMS and CMS(s) and the generic applicant is not applying for more indications than those authorised for the reference medicinal product in the RMS, the legal basis for the application should be Article 10(1) of Directive 2001/83/EC in all involved MSs (RMS and CMSs) and not a mixture of Articles 10(1) and 10(3) depending on the indications approved nationally for the reference medicinal product in the CMS(s).

Article 10(3) is intended to ensure that in cases where the medicinal product does not fall within the definition of a generic medicinal product or does not fulfil the other criteria mentioned therein, the Applicant is requested to generate its own data to bridge the gap with the reference medicinal product, which is not required in the above mentioned situation.

Applicants are advised to discuss such situations with the RMS ahead of submission of the application for marketing authorisation and to address it in the respective cover letter.

For information on the processing of generic applications when the generic has more indications or fewer indications than the reference product in the CMS, please refer to the CMDh agreement on this issue, published on the CMDh website, under Procedural guidance, Generics http://www.hma.eu/211.html.
Possibility to use a Medicinal Product authorised in a Member State prior to its accession to the EU as Reference Medicinal Product for the purpose of the data exclusivity period

6. Is a medicinal product authorised in a Member State prior to its accession to the EU eligible to be reference medicinal product? How do the data protection rules apply?

It has been agreed with the CMDh that a reference medicinal product must meet the following cumulative criteria:

- It should be (or have been) authorised in the European Union; i.e. for medicinal product authorised in countries prior to their accession to the European Union, the date of accession of the country concerned.
- It must be authorised in accordance with the Acquis Communautaire. This implies that the dossier of the medicinal product has been updated to comply with the Acquis Communautaire.
- And the relevant data exclusivity period has to be expired.

The starting date for the purposes of counting the period of data protection is therefore linked to the date of authorisation of the reference medicinal product in accordance with the Acquis in the territory of the European Union.

In practice, it means that two scenarios are possible: either a medicinal product was authorized according to the Acquis Communautaire, as of the date of accession, (see a)) or the medicinal product was brought in compliance with Acquis Communautaire in the transitional period following accession (see b)):

a) For a medicinal product authorised in a MS before its accession to EU but according to the Acquis Communautaire requirements on MA application (dossier-modules 1-5), the data protection period will be counted as of the date of accession to EU.

b) For a medicinal product authorised in a MS before its accession to EU but not authorised according to the Acquis Communautaire at that time, the medicinal product is not eligible to be a reference medicinal product unless it is granted a Marketing Authorisation according to the Acquis Communautaire in the new EU MS (after accession). The data protection period for this medicinal product will be counted as of the date of the Marketing Authorisation which has been granted in compliance with the Acquis Communautaire.

As a general principle, it should be noted that in order to maintain the MA for medicinal products in the new accessing countries after accession to the EU, the MA needed to be granted in accordance with the Acquis Communautaire at the time of accession. However, some of the MS that joined the EU on the 1st May 2004 were granted a transitional period for specific Marketing Authorisations (see NtA, Chapter 1, “Reference medicinal product”). The National Competent Authorities of these countries should be contacted to get information on the exact date on which a MA according to the Acquis Communautaire has been granted for a particular product. Marketing Authorisations granted in other member states are automatically considered to be in accordance with Acquis Communautaire as of the date of accession while no transitional period was required.
Compliance with commission decisions after referral procedures

7. How can compliance with the Commission Decision be achieved for generics following an Article 30 referral procedure?

Generic companies should submit a variation under category C.I.1.b) if no additional data is submitted by the MAH, or a Type II Variation, category C.I.1.c) if additional data is submitted by the MAH to change the product information in accordance with the outcome of the Article 30 referral procedure for the reference medicinal product.

It is recommended that the variation application is submitted within 90 days after the publication of the Commission Decision.

Reference products for bioequivalence studies

8. Can a medicinal product, which is not licensed in the EEA, be used as Reference Product in bioequivalence studies?

A medicinal product to be used as a reference in a bioequivalence study conducted in support of a generic/hybrid application must be a version of the original medicinal product that is authorised within the Community. Consequently bioequivalence studies performed with a product not authorised within the EEA will not be considered acceptable.

8.a. In situations where the relevant strength of the reference product is not available in any Member State (because it is no longer marketed), is it possible to submit an Art 10(1) application for a generic product which uses another generic product as the reference product for the bioequivalence study?

As per Notice to Applicants chapter 1, a generic product referring to a generic product is not possible and therefore it is not possible for an applicant to use another generic product as the reference product in a bioequivalence study to support a generic application (Article 10(1)), even if the relevant strength of the reference product is not available because it is no longer marketed.

In situations where the applicant has definitively established that the relevant strength of the same pharmaceutical form of a reference product is not available in the EU, it may be possible for the applicant to use:

(i) a different strength of the same pharmaceutical form of the reference product or if not available;

(ii) a different pharmaceutical form (e.g. a different immediate-release oral pharmaceutical form) of the reference product other than that applied for as the reference product for the bioequivalence study to support a generic application.

In general the cumulative strength of the reference product should be the same as the strength that the applicant has applied for, thus maintaining the direct link with the reference product. However it may be justified to use different strengths when pharmacokinetics are linear and a potency correction is performed. This would apply if the different strengths or pharmaceutical forms of the reference product are part of the same Global Marketing Authorisation and the general biowaiver criteria as outlined in section 4.1.6 of the Guideline on the Investigation of Bioequivalence.
The acceptability of using a different strength or pharmaceutical form of the reference medicinal product should also be discussed with the competent authority of the country where the reference product is authorised.

Alternatively, if a suitable reference product cannot be obtained to conduct a bioequivalence study to fulfil the requirements of Art 10(1), the applicant should consider using a different legal basis for the application, e.g. an article 10(3) application. The dossier submitted by the applicant must fully support the chosen legal basis.

Naming of generics

9. Does the requirement in Article 3(3)c of Regulation (EC) No 726/2004 that a generic of a reference medicinal product authorised by the Community should be authorised under the same name in all Member States where the application has been made apply to generic applications submitted via the Mutual Recognition or Decentralised Procedures?

Article 3(3)c of Regulation 726/2004 allows for a generic medicinal product of a reference medicinal product authorised by the Community to be authorised under the condition that it has the same name in all Member States where the application has been made. Therefore, the name of a generic of a centrally authorised reference medicinal product should be the same in all Member States where it is authorised, regardless of the procedure followed for authorisation, i.e. centralised, mutual recognition or decentralised procedure and throughout the life cycle of the product.

In accordance with Directive 2001/83/EC, Article 1(20) the name of a medicinal product may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the MAH. The common name is the INN recommended by the WHO, or, if one does not exist, the usual common name.

For the purposes of the provision stated in the Regulation, all the linguistic versions of the INN shall be considered to be the same.

The name of the marketing authorisation holder within the name of the medicinal product should correspond to all or part of the official name of the marketing authorisation holder as presented in the proof of establishment of the applicant/MAH.

All the linguistic versions of the name of the MAH shall be considered to be the same.

For further advice, see also Q&A 9a, 9b, 9c.

9a. Invented name of generic of a reference medicinal product authorised by the Community. Are there any circumstances where the use of a different name for a generics of a reference medicinal product authorised by the Community, Regulation 726/2004, Article 3(3)c shall be allowed in one or more Member States (MS) concerned?

In exceptional cases:

- the use of a different name (invented or a common or scientific name accompanied by a trade mark or the name of the MAH) in a Member State may be allowed where the proposed invented
name has been cancelled, opposed or objected to under trade-mark law in a Member State. Satisfactory evidence of this should be provided.

- the use of a different name (invented or a common or scientific name accompanied by a trade mark or the name of the MAH) may be allowed if the MAH is not the same in each Member State and the MAH in one or more Member State is not the owner of the trademark. Satisfactory evidence that the MAH in a Member State is not the owner of the trademark should be provided.

9b. Invented name for a generic of a reference medicinal product authorised by the Community. What should applicants do to facilitate agreement of an invented name in all Member States concerned in the MRP or DCP?

In order to facilitate agreement of an invented name in all Member States in MRP or DCP, the applicant should:

- check the national markets before submission of their application to avoid similarities in invented names being proposed;
- for DCP, at the time of submission, in addition to the invented name proposed by the applicant, submit at least one additional name and up to three additional names in order to offer alternatives to Member States involved in the procedure. The applicant should indicate their preferred invented name in order of priority. This information should be included in Annex 5.19 of the MAA form.

9c. Common or scientific name accompanied by a trade mark or the name of the MAH. For MA applications where the MAH is not the same in each Member State concerned (as is permitted in MRP/DCP), and using the INN accompanied by MAH product name format, how should the name in each Member States be implemented in practice?

For MA applications where the MAH is not the same legal entity in each Member State concerned and using the INN accompanied by MAH product name format, the name of the MAH used in the product name should be that proposed in each Member State.

For example:

**RMS:** SE

**CMS:** DE, FR, IE, NL, NO, PL

SE & DE: MAH1;
FR, IE, NL, NO: MAH2;
PL: MAH3

Product name would be:

SE & DE: INN+MAH1
FR, IE, NL, NO: INN+MAH2;
PL: INN+MAH3
10. **Following a successful concluded MRP/DCP, a Generic of a reference medicinal product authorised by the Community is authorised in all MSs concerned with the same name. Is it possible to change the name of the Generic following the transfer of the MA in one or several MS(s) to a new MAH?**

If the name of the MAH is part of the name of the Generic (e.g. INN-MAH) and the MA is transferred to a new MAH in one or several, but not all MS, a change of the name of the Generic (e.g. INN-new MAH) could be necessary. Similarly, if the original approved name is an invented name or trademark and the ‘new’ MAH is not the owner of that name, then a different invented name or trademark may be allowed for the transferred MA. In the case a change of the name of the generic is necessary, this has to be done as a variation in line with the requirements of Commission Regulation (EC) 1234/2008.

**Legal basis for Products for Local Use**

11. **What should be the appropriate legal basis for an application for marketing authorisation where bioequivalence cannot be demonstrated through bioavailability studies, such as for products for local use intended to act without systemic absorption after e.g. oral, nasal, inhalation, ocular, dermal administration?**

The CMDh has conducted a questionnaire to collect Member States views on this issue and agreed on the following recommendations:

- Applications for marketing authorisation for products for local use should be submitted according to Article 10.3 of Directive 2001/83/EC;
- The submission of the results of the appropriate pre-clinical tests or clinical trials OR justification for its absence depends on the need for bridging vis-à-vis the reference medicinal product and will be assessed during the evaluation of the application.

On this regard, the CMDh notes the information included in the Notice to Applicants, Volume 2A, Chapter 1 that "where bioequivalence cannot be demonstrated through bioavailability studies, for example for locally applied and locally acting drugs, Article 10(3) requires that the results of appropriate pre-clinical tests or clinical trials shall be provided and this Article provides the correct legal basis for the application."

The note for guidance on the clinical requirements for locally applied, locally acting products containing constituents (CPMP/EWP/239/5) defines the clinical requirements for locally applied, locally acting products with a known active substance.

Locally acting products are products which are applied locally and are assumed to exert their effect at the site of the application. Examples are dermatological products (e.g. creams, ointments), inhalational products like powders or aerosols for inhalation, eye drops, ear drops, nasal products, but also other products which act locally.

It is necessary to show for locally acting products that the product to be approved (either a generic or reformulated product) is therapeutically equivalent to the product already approved (based on a full dossier).

In order to demonstrate therapeutic equivalence, clinical trials are in principle necessary, but other models may be used. For this purpose, depending on the situation, human pharmacodynamic studies,
local availability studies, animal studies or in vitro can be used, provided that all studies used are adequately validated and adequate justification is given for the absence of data.

For orally inhaled products (OIP), please refer to the Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev.1).

When to submit a Generic/Hybrid Application referring to a Centrally Authorised Reference Product

12. When can I submit my generic/hybrid application considering the protection period of the reference medical product?

The same answer as indicated in the EMA Q&A Generic/hybrid applications No.12 applies.

At the time of submission of the generic/hybrid application, the protection period of the reference medicinal product should have expired in order to allow the applicant to rely on the dossier of the reference medicinal product.

For generic/hybrid application submitted through the MR/DC procedure, when referring to:

- a centrally authorised reference medicinal product, the 10-year or 8-year protection period, as applicable, should have expired; the relevant protection period should be counted as starting from the date of notification of the marketing authorisation decision to the MAH and can be found in the Official Journal of the European Union as well as in the Community register of medicinal products for human use on the European Commission website; as an example, a generic application of a reference medicinal product notified on Day A, could be submitted 10 or 8 years later than Day A+1, as applicable;

- a nationally authorised reference medicinal product, the 6/10-year protection period, depending on the Member State which has granted the marketing authorisation or 8-year protection period, as applicable, should have expired.

Notion of ‘global marketing authorisation’

The calculation of the protection period should take into account the notion of global marketing authorisation.

The global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical forms, administration routes or presentations authorised through separate procedure and under a different name, granted to the marketing authorisation holder of the initial authorisation.

This means that for a reference medicinal product, the start of the data exclusivity and market protection periods is determined by the first MA in the Union which was granted in accordance with the relevant European pharmaceutical legislation (Acquis Communautaire).
In case of any doubt, the applicant can liaise with the National Competent Authorities provided detailed information are given.

The new protection periods of ‘8+2+1’ applies only to reference medicinal products for which the marketing authorisation application has been submitted as of 30 October 2005 for MRP, DCP and national procedures and as of 20 November 2005 for centralised procedure according to the revised European Legislation.

In line with the revised rules mentioned above, applications for generic/hybrid medicinal products can be submitted after expiry of the data exclusivity period for the reference medicinal product i.e. 8 years after the date of notification of the authorisation of the reference medicinal product to the MAH. However, the authorised generic/hybrid product can only be placed on the market 10 or 11 years after expiry of the market exclusivity period applicable for the reference medicinal product.

**European Reference Medicinal Product (ERP)**

**13. How to select the European Reference Medicinal Product (ERP) for Concerned Member States (CMS) those have never had the Reference Medicinal Product approved?**

In case the Reference Medicinal Product is/has been authorised in the RMS but not in the CMS, it is recommended to use the product authorised in the RMS as ERP in the CMS. In case the ERP is chosen from another Member State, the competent authority of that Member State has to provide the minimum information for the ERP within one month upon request of the RMS, which can lead to unnecessary delays during the validation period.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Chapter 1 (section 6), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A
- Community register of medicinal products for human use

**14. Which legal basis should be used if the strength and/or the pharmaceutical form of the reference medicinal product is not approved in all MS concerned?**

If a strength and/or pharmaceutical form of the reference medicinal product is not approved in all MS concerned the CMDh recommend the use of an ERP and the legal basis Article 10(1) in all MS concerned instead of the mixed legal basis Article 10(1) and Article 10(3). This approach might facilitate both the submission and the maintenance of the product. In the application form, the applicant should tick the box for Article 10(1) for all MS concerned of the procedure in accordance with the principle of using ERP.

In the past, applications with mixed legal basis Article 10(1) and Article 10(3) were accepted. For these medicinal products, there is no exemption for the obligation of the MAH to submit PSURs for MAs authorised under Article 10(3) even if the legal basis in RMS is Article 10(1) and PSURs for the active substance are not required for MAs authorised under Article 10(1).