

CMD(v)/GUI/014

GUIDANCE

for

The Processing of Generic Applications Through MRP / DCP

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1. INTRODUCTION

Directive 2004/28/EC, which amended Directive 2001/82/EC, increased the scope for making generic based applications. Some of the principles introduced are fundamentally different from those previously followed, for example the lowest common denominator approach where only common species and indications were taken along with all of the warnings and the highest withdrawal period.

The European Commission has issued guidance to CMD(v), which have been subsequently endorsed at the Lisbon meeting of the HMA, held in July 2007.

2. AIM AND SCOPE

This GUI is intended to give guidance to Member States on the approach to be taken for generics in order to help facilitate a smooth passage through the regulatory process.

3. REFERENCES AND RELATED DOCUMENT

This Guidance should be read in conjunction with:

CMD(v)/BPG/001	Best Practice Guide for Veterinary Mutual Recognition Procedure.
CMD(v)/BPG/002	Best Practice Guide for the Decentralised Procedure.
CMD(v)/SOP/001	Standard Operating Procedure Disagreement in Procedures – Referral to CMD(v).
CMD(v)/BPG/010	Best Practice Guide for the Reference Member State
CMD(v)/GUI/006	Documentation to be Submitted by a Member State When Reference Medicinal Product is Not Authorised in the RMS.

Guideline on the definition of a potential serious risk to human, animal health or for the environment. (www.ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev5.htm)

CMD(v)/GUI/003 Management of emails during a procedure

CMD(v)/BPG/008 Automatic validation of applications.

Articles 5 and 13 of Directive 2001/82/EC, as amended.

Volume 6A of the Notice to Applicants.

<http://www.emea.europa.eu>

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4. GENERAL PRINCIPLES

The following are **general** principles intended to set out how Member States will interact with each other and deal with generic applications being considered through a European procedure. They are not intended to preclude Member States from pursuing a referral procedure where they are convinced that there is a serious public health risk.

- The Member States will accept the SPC of the Reference Product which usually is that of the Reference Member State (RMS). The SPC of the Reference Product may include additional indications, species and routes of administration as well as a different withdrawal period compared to the originator product in the Concerned Member State (CMS). Nevertheless these differences should be accepted unless there are justified grounds for refusal based on a potential serious risk.
- The Member States should accept the European Reference Product (ERP) based on mutual trust by recognising the assessment performed by the Member State which has authorised the ERP according to the data requirements and standards in force at the time of the application.
- When a CMS has within its territory a product authorised by the same applicant, as the national reference product, that CMS may take into account the knowledge it has gained from its original assessment and subsequent PSUR information. This information may be utilised when making the decision to authorise the generic product.
- The extent of data / information exchange should be proportionate and restricted only to the principle of minimum data exchange. The assessment report prepared by the RMS in respect of the original reference product, whenever possible and if available, or the confidential annex prepared by the RMS, should be sufficient to allow the Concerned Member States to agree to an authorisation without requesting further data or documentation. The need for further documentation should be the exception rather than the rule and be fully justified.
- The RMS will ensure that it provides an assessment of the relevant data on the reference product where there are significant differences between SPCs in other CMS e.g. species and indications, based on information submitted by the applicant.
- Where a potential serious risk is identified in relation to efficacy or safety (except safety to the environment), a CMS can request additional clarification /documentation from the RMS on the reference product, particularly if that CMS has previously refused an indication, species or similar product.
- The vertical harmonisation between the SPCs of the reference and generic products should be encouraged. However, in the event of safety concerns or potential serious risk to human/ animal health or for the environment the harmonisation should be enforced.
- Each application for a generic product must contain an Environmental Risk Assessment (ERA).
- As with all nationally authorised medicines, National Competent Authorities are accountable in the event that any efficacy or safety issues later arise with regard to

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the generic product authorised. Therefore, NCA's must be in a position to satisfy themselves regarding the quality, safety and efficacy of all medicinal products on their markets.

5. DEFINITIONS

5.1 Article 13 of the Directive

Article 13 of the Directive provides the definition of a generic veterinary medicinal product. This will mean that the product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference product, and whose bioequivalence with the reference medicinal product has been demonstrated by bioavailability studies.¹

5.2 Data Protection

The reference product benefits from at least ten years of data protection. Generic applications can be applied for after eight years of data protection. However this only applies to reference products authorised after 30 October 2005 and will therefore come into effect as from October 2013. A Marketing Authorisation (MA) can be issued but the holder of the Generic MA cannot place their product on the market until the full ten years of data protection have elapsed. These MAs will be issued with a condition that they cannot be marketed until the data protection period has passed.

The ten year protection period can, however, be extended by one year for each extension to the marketing authorisation to include additional food producing species, to a maximum of 13 years.

However this will only be possible:

- i. where the extension applications are made within the first five years of authorisation of the product,
- ii. the product must also contain a new active substance not previously authorised in the Community before 30 April 2004 and finally
- iii. in the case of products for food-producing species that the Marketing Authorisation Holder (MAH) also applied for the determination of the MRL for the species covered by that product.

All three conditions must be met before the extended period of protection is allowed.

A protection period of 13 years is automatically given to products authorised for use in fish or bees.

The new rules on data protection as defined in the amended legislation only apply to products authorised after the implementation of the legislation i.e. 30 October 2005. Any products authorised before that date will only benefit from a maximum of 10 years or 6 years

¹ The various immediate release oral pharmaceutical forms shall be considered to be one and the same. Also in some situations generic products are exempt from demonstrating bio-equivalence.

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of protection depending on the legislation in the respective Member States, subject to the application of the global marketing authorisation principle.

5.3 Reference Product

The Reference product is the product authorised in the RMS/CMS which the generic application is referring to. The generic applicant may use a reference product authorised in another Member State to demonstrate bio-equivalence, as long as the products are the same.

Furthermore, the amended legislation now permits the reference product to have been authorised at some point. There is no longer a requirement for the reference product to be authorised at the time of the application of the generic product. All reference products must have been authorised using a full data package in accordance with the Directive in force at the time of authorisation. It is not possible to have a generic application citing a generic reference product.

5.4 European Reference Product

The European Reference Product (ERP) is a product which is or has been authorised as a full application somewhere in the Community in accordance with the Directive in force at the time of authorisation. It is possible for a generic applicant, including hybrid applications, to cite an ERP. The ERP must meet all the rules relating to data protection but it means that Member States can accept an application based on a product for which it does not have a national reference product authorised.

On receipt of the request the authorising Member State of the ERP has 30 days to provide the full composition of the reference product and other necessary relevant documentation as defined in the CMD(v) guidance document GUI 006. The principle is of minimum data exchange and therefore it is not possible to request a full data package. On receipt of this information some documentation of the ERP may need to be translated before any assessment can begin.

In MRP procedures it is the duty of the RMS to provide the minimum information according to CMD(v) GUI 006 at the absolute earliest convenience to promote the conditions for CMS assessment.

5.5 Global Marketing Authorisation

Article 5 of the Directive introduces the concept of the global marketing authorisation. When a veterinary medicinal product has been granted an initial authorisation any subsequent authorisations issued to that Marketing Authorisation Holder for products containing the same active substance, for example additional species, strengths, pharmaceutical forms, administration routes, and presentations, as well as any variations and extensions, shall be considered as belonging to the same global marketing authorisation. This means that for practical purposes the start of the data protection period is the date at which the initial authorisation is granted.

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5.6 SPC of the Reference Product

The major issue for generic applications undergoing Mutual Recognition or the Decentralised Procedure is usually the disagreement caused by the differences in the SPCs of similar national products authorised in the CMSs.

However the principle applied is that the SPC of the reference product authorised in the RMS should be accepted by all the CMSs regardless of the differences in the local SPCs.

The Commission has endorsed this approach and this includes additional indications and species. The Commission has also endorsed the principle of minimum data exchange built on co-operation and proportionality. The assessment summary based on the data of the reference product contained in the dossier of the RMS should be sufficient to allow the Concerned Member States to agree to an authorisation without requesting further data or documentation. The need for further documentation should be the exception rather than the rule.

5.7 Hybrid Applications

This is covered under Article 13(3) of the Directive. The results of appropriate tests and trials shall be provided in cases where the application does not:

- i. fall under the strict definition of a generic product, or
- ii. where it is not possible to demonstrate bio-equivalence to the reference product, or
- iii. where there are changes to the active substance, therapeutic indications, strength, pharmaceutical form or route of administration from the reference product.

In practical terms this means that the applicant can cite a reference product but needs to provide bridging data to account for the differences between the proposed product and the reference product. However, it is not possible for an applicant to submit a hybrid application that deletes or adds an active substance to that of the reference product cited.

5.8 Confidential annex to the Assessment Report

This annex provided by the RMS is a report that comments on additional indications, species, routes of administration and differences in the withdrawal periods from the SPC of the reference product with those authorised in the CMSs. This may simply be the assessment report prepared for the reference product or another document prepared by the RMS commenting on the data submitted in respect of the reference product. The confidential annex must not be sent to the applicant of the generic application and is a document that remains confidential between National Competent Authorities.

6. VALIDATION

Validation of the generic applications by the RMS and CMS is the same as for other Mutual Recognition or Decentralised applications. Applicants should follow the national validation requirements as set down in Chapter 7 of Volume 6A of the Notice to Applicants. In addition the applicant must provide a summary table detailing the differences between the various SPC authorised by the RMS and CMS – see Annex 1. This summary will be vital in helping

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the RMS to identify areas which the RMS will need to address in order to provide assurance to the CMSs and also to help the CMSs notify the RMS of areas that they in turn would need to be addressed. The summary table should also be made available to the RMS at least 3 months in advance of the planned start date.

This table should focus on:

- Pharmaceutical form(s)
- Strength(s)
- Target species
- Contra-indications
- Environmental warnings
- User warnings

For each species:

- Routes of administration
- Indications
- Dose and duration of treatment for each indication
- Withdrawal period where relevant.

It should be noted that the start of the validation period may be delayed in cases where a European Reference Product is being cited without being authorised in the RMS. Validation will commence when the RMS and CMS receive the required minimum information from the authorising Member State.

7. PROCEDURES

a) Mutual Recognition and Decentralised Procedure – National Reference Products Authorised

RMS – DCP applications

The RMS, using the SPC summary table provided by the applicant, will need to identify those areas which the CMSs may need to have addressed. This is done by completing an annex to the main assessment report. It should be noted that the assessment report is sent to the applicant and therefore any reference to the original data submitted in respect of the reference products must be contained within a separate confidential annex which is not sent to the applicant. This annex would be circulated to the CMSs with the assessment report at day 70 of the DCP. The confidential annex may simply be the assessment report prepared in respect of the reference product.

Any further questions submitted by the CMSs relating to the SPC differences can then be addressed by updating this confidential annex between day 106 and 120. These questions will not be included in the List of Questions to the applicant but should be presented in a separate document.

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RMS – MRP applications

The RMS, using the SPC summary table provided by the applicant, will need to identify those areas which the CMSs may need to have addressed. The differences between SPCs are addressed by completing an annex to the main assessment report. It should be noted that the assessment report is sent to the applicant and therefore any reference to the original data submitted in respect of the reference products must be contained within a separate confidential annex. This annex would be circulated along with the summary table mentioned in section 6, provided by the applicant, to the CMSs prior to the start of the MRP timetable of 90 days. The confidential annex may simply be the assessment report prepared in respect of the reference product.

Any areas not covered, which have been raised by the CMSs during the validation phase or shortly after procedure start, will need to be addressed by the RMS by updating the confidential annex which is circulated to the CMSs at Day 64 of the MRP along with the applicant's responses to the List of Questions.

CMS - DCP applications

The CMS is during validation encouraged to notify the RMS of any areas that they would wish the RMS to cover within the assessment report or within the confidential annex to the assessment report. The summary table provided will help the CMS to accomplish this and will also help to put the authorisation of this product into wider context. For example the CMS will be able to tell if they are the only one not to have authorised a particular indication – this would help to provide greater assurance that comes with multiple authorisations and subsequent pharmacovigilance programmes.

Where the proposed SPC of the generic product includes additional indications, species, routes of administration or different withdrawal period, these should be accepted by the CMS based on the RMS assessment summary. This is based on the principle of mutual trust. Any request for additional supporting data from the RMS should be an exception. The CMS may have grounds for seeking additional clarification / documentation if the product has previously been refused in the CMS or if the proposed SPC of the generic product contains an indication or species that has previously been refused by the CMS. Any such request should be made via email and be fully justified.

Any areas not sufficiently covered by the RMS should be notified to them as part of the CMS comments provided during days 70 – 100.

CMS – MRP applications

In the given timelines of the MRP applications it will not be possible for the CMS to identify issues before the RMS has updated its assessment report. However, such issues should be brought forward during validation or shortly after procedure start at the latest by the CMS for the RMS to update the confidential annex to supplement the applicant's responses to the day 54 questions. The summary table provided will help the CMS to help to put the differences between the SPCs into context and to see how the product is authorised across the various

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Member States. This will help the CMS to quantify any potential serious risk issue and to put it into a wider perspective. For example the CMS will be able to tell if they are the only one not to have authorised a particular indication – this would help to provide greater assurance that comes with multiple authorisations and subsequent pharmacovigilance programmes.

Where the proposed SPC of the generic product includes additional indications, species, routes of administration or different withdrawal period, these should be accepted by the CMS based on the RMS assessment report. This is based on the principle of mutual trust. Any request for additional supporting data from the applicant or the RMS should be an exception. The CMS may have grounds for seeking additional clarification / documentation if the product has previously been refused in the CMS or if the proposed SPC of the generic product contains an indication or species that has previously been refused by that CMS. Any such request should be made via email and be fully justified.

Any areas not sufficiently covered by the RMS should be notified to them as part of the CMS comments provided at day 54.

b) Mutual Recognition and Decentralised Procedure – European Reference Product

RMS – MRP / DCP applications

The European Reference Product can only be used in the CMSs where a national reference product has not been authorised. If a suitable authorised reference product exists, it must be used. See also section 5.4 – European Reference Product.

A Member State may be asked to act as the RMS for a generic product which cites a European Reference Product not authorised within its territory. Before accepting such a procedure the proposed RMS should discuss the issue with the applicant.

The applicant should be advised of the constraints of choosing an RMS who has no prior knowledge of the product and the difficulties that the RMS faces in defending the product to other CMSs and at CMD(v). Therefore it is strongly recommended to use the MS where the ERP is authorised as RMS. Applicants should be advised of the benefits of using the DCP.

In the case of an ERP the RMS needs to receive the minimum information as detailed in CMD(v)/GUI/006 (Documentation to be Submitted by a Member State When Reference Medicinal Product is Not Authorised in the RMS) before the application can be validated. The authorising Member State has 30 days to provide the required documentation. Validation cannot progress until this information has been received and the information translated if necessary.

Any CMS comments would need to be addressed by updating the confidential annex after day 54 of MRP or between days 106 – 120 for DCP.

CMS - MRP / DCP applications

The CMS is during validation encouraged to notify the RMS of any areas that they would wish the RMS to cover within the assessment report or within the confidential annex to the assessment report.

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Any request for additional supporting data from the applicant or the RMS should be an exception. The CMS may have grounds for seeking additional clarification / documentation if the product has previously been refused in the CMS or if the proposed SPC of the generic product contains an indication or species that has previously been refused by that CMS. Any such request should be made via email and be fully justified.

Any areas not sufficiently covered by the RMS should be notified to them as part of the CMS comments at day 54 of MRP or provided during days 70 – 100 of DCP.

c) Referrals

If any disagreement on the assessment report, SPC, labelling and package insert remains between the RMS / CMS on the grounds of a potential serious risk, following the CMD(v) 60-day referral procedure, the matter will be referred to the CVMP (The Committee for Medicinal Products for Veterinary Use) for arbitration.

The decision of the European Commission, following a referral procedure in CVMP, is binding in all Member States.

Any referral of a generic product to the CVMP under Article 33(4) should be restricted to issues regarding quality, bioequivalence, injection site residues, if appropriate, and environmental risk. It is not possible to refer a generic application under Article 33(4) if the dissenting CMS(s) has concerns over the safety and efficacy of the reference product, as this is outside of the framework for an Article 33(4) referral for generic applications. Notification of disagreement on issues that are outside of the framework of a 33(4) referral may either lead to a recommendation to grant a marketing authorisation or a rejection of the referral notification.

Where a Concerned Member State observed a potential serious risk in relation to the efficacy or safety of the reference product they should consider triggering a referral under Article 34 or Article 35 of the Directive. Any proposed referral under these articles should be first discussed with the EMEA to ensure the appropriate legal base is used.

Article 34 referral

An Article 34 procedure can be initiated when different decisions have been taken on the same (reference) product. The procedure will result in a fully harmonised SPC of the (reference) product in the Member States. Consequently CVMP will also consider the divergent SPC parts which were not the subject to disagreement in CMD(v). Generics are not directly covered by the scope of the referral, but MS can take national follow-up measures following the opinion.

Article 35 referral

If regarding the (reference) product an interest for the European Community can be substantiated, an Article 35 procedure can be initiated. In comparison with an Article 34

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referral, the Article 35 procedure can cover the reference product as well as other products of the same class, including their generics. Where the procedure covers a class of products, the scope of CVMP's examination can be limited to the SPC parts relevant to the substantiated community interest.

If Member States feel that a potential risk is felt so serious that it requires immediate action, it should refer the generic (still going through MRP / DCP) and the reference product (and if necessary other related products) under Article 35 of the Directive. All Member States involved should also consider suspending the reference product, if one was authorised and any other related products.

8. ABBREVIATIONS

AR	Assessment Report
BPG	Best Practice Guide
CMS	Concerned Member State
CVMP	The Committee for Medicinal Products for Veterinary Use
DCP	Decentralised Procedure
ERA	Environmental Risk Assessment
ERP	European Reference Product
GUI	Guideline
HCD	Highest Common Denominator
HMA	Heads of Medicines Agency
LCD	Lowest Common Denominator
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MUMS	Minor Uses or Minor Species
MRL	Maximum Residue Limit
MRP	Mutual Recognition Procedure
MS	Member State
RMS	Reference Member State
RP	Reference Product
SPC	Summary of Product Characteristics
VMP	Veterinary Medicinal Product

Reference product:									
Presentations in Member States									
MS	Product Name & Pharmaceutical form(s)	Strength(s)	Indication(s)	Target species	Routes of administration	Dose and duration of treatment	Withdrawal period(s) if appropriate	Contra-indications	Environmental warnings
AT									
BE									
BG									
CY									
CZ									
DE									
DK									
EE									
EL									
ES									
FI									
FR									
HU									
IE									
IS									
IT									
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UK									