CBG MEB

MEDICINES EVALUATION BOARD

Policy document
Duplex marketing authorisation

MEB 16

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1. Contents

2. Abbreviations and definitions

ASMF	Active Substance Master File
CBG	Medicines Evaluation Board
CEP	Certificate of Suitability
CESP	Common European Submission Portal
CMS	Concerned Member State
DC	Decentralised
eCTD	Electronic Common Technical document
EER	European Economic Area
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
MR	Mutual Recognition
MRP	Mutual Recognition Procedure
PSMF	Pharmacovigilance System Master File
RMP	Risk Management Plan
RMS	Reference Member State
RVG	Register Packaged Medicinal Products
SmPC	Summary of Product Characteristics

3. Introduction

A duplex marketing authorisation is a marketing authorisation for a medicinal product, for which the dossier at the time of the application for the marketing authorisation is identical to that of a previously registered medicinal product. The only differences are the marketing authorisation holder, the name of the medicinal product, the RVG number, the person responsible for communication on behalf of the marketing authorisation holder and the person responsible for pharmacovigilance, the (summary of the) Pharmacovigilance System Master File and the lay-out of the mock-up and package leaflet.

4. Purpose and scope

The duplex marketing authorisation stands on its own, with the exception of a duplex with further conditions (see section 7). Once this marketing authorisation has been granted, the marketing authorisation holder can implement variations in the dossier. This does not apply to a duplex with conditions. The marketing authorisation holder of a duplex marketing authorisation must also meet all obligations set out in the Medicines Act.

The legal basis for the duplex medicinal product is the same as the legal basis of the medicinal product on which the duplex is based.

To be eligible for a duplex marketing authorisation, the duplex medicinal product and the medicinal product on which the duplex marketing authorisation is based must meet certain conditions. The submission of specific documentation is also mandatory. For more information, please refer to section 5 of this policy document.

The MEB will not assess the content of a duplex marketing authorisation, in order to facilitate swift issuing of a marketing authorisation (within 45 days). These 45 days do not include any clock-stop period.

As with an ordinary national marketing authorisation, a mutual recognition procedure (MRP) for a duplex marketing authorisation can only be started once it has been confirmed that the dossier meets all the current dossier requirements for new applications.

In the subsequent sections, the product for which the application for a duplex marketing authorisation is requested will be called the "duplex medicinal product" or "product A" and the duplex applicant (the future authorisation holder) will be called "(legal) person A". The medicinal product that is already authorised will be called the "reference product" or "product B" and the authorisation holder of that product will be called "(legal) person B".

5. Procedure/Assessment criteria

5.1 Conditions relating to the duplex product and reference product

In order to be eligible for a duplex marketing authorisation, the duplex medicinal product must meet the conditions listed under §5.1.2 and the medicinal product on which the duplex marketing authorisation is based must meet the conditions listed under §5.1.1.

If one or more of the conditions listed below are not met, the MEB will inform the applicant together with any other objections against the duplex application and will implement a

clock-stop for the application procedure. Once the responses to the objections have been submitted, the processing of the application will resume.

5.1.1 Conditions relating to the reference product

1. The reference product has not been granted a marketing authorisation via the centralised procedure.
2. The reference product has not been granted a marketing authorisation via the duplex procedure.
3. The reference product has not been granted a marketing authorisation via the informed consent procedure.
4. The reference product has a valid marketing authorisation, which was granted via the national procedure or DC/MR procedure.
5. The reference product was granted a marketing authorisation no more than 5 years ago, or the reference product completed an NL=RMS MRP successfully no more than 5 years ago (day 90 is ≤ 5 years ago).
6. The legal basis of the reference product is known and recorded by the MEB.
7. If the reference product concerns an NL=CMS authorisation, then legal persons A and B must not be the same or affiliated to each other.
8. The reference product has an Environmental Risk Assessment (ERA) that complies with the current version of the ERA guideline (Guideline on the environmental risk assessment of medicinal products for human use).
9. The reference product has an approved Risk Management Plan (RMP).

Ad 1: A duplex marketing authorisation involves national policy and can only be followed for reference products with a national marketing authorisation that was granted via the strict national application procedure or MR/DC procedure.

Ad 2: If the reference product itself has been authorised via the duplex procedure, then there is a chance that the original reference dossier - on which the authorisation is based - is older than 5 years. Even if the reference dossier for the current duplex application was authorised less than five years ago, the duplex application is still effectively based on a dossier that last underwent complete assessment more than 5 years ago.

Ad 3: If the reference product itself has been authorised via the informed consent procedure, then there is a chance that the original dossier - on which the authorisation is based - is older than five years. Even if the reference dossier for the current duplex application was authorised less than five years ago, the duplex application is still effectively based on a dossier that last underwent complete assessment more than 5 years ago.

Ad 5: "Successfully completed" refers to a mutual recognition procedure with the Netherlands as Reference Member State (RMS) that resulted in a marketing authorisation in one or more Concerned Member States (CMS).

Ad 7: The condition - that the reference product may not be authorised via the DCP or MRP if NL = CMS - applies in the case where the marketing authorisation holder for the reference product and the duplex applicant are the same (legal) person or are affiliated to each other:

- From a legal point of view, a CMS cannot recognise the marketing authorisation issued by the RMS more than once. A request for a copy of a dossier from the same marketing authorisation holder must therefore always be submitted to the country where the authorisation was issued for the first time (RMS). This means that, if the original marketing authorisation was first awarded in a country other than the Netherlands, the duplex procedure is not possible. An exception applies if the marketing authorisation holder for the reference product is not the same as the duplex applicant. In that case, the duplex procedure is possible.
- As has been stated in Commission communication no. 98/C 229/03, companies are considered to be the same if they belong to the same parent or group of parent companies, or if there are concluded agreements (e.g. “licensees”)’ or if ‘concerted practices’ regarding marketing pharmaceuticals are involved. Any form of cooperation between two companies as part of a duplex application does not automatically warrant the conclusion of "concerted practice" (please refer to the ruling by the Council of State in the appeal by GlaxoSmithKline B.V. against the ruling by the Utrecht District Court on 15 May 2003 (dated 21 July 2004)).

For more information, please refer to the CMDh (Coordination Group for Mutual Recognition and Decentralised Procedures human) document entitled ‘Recommendations on multiple/duplicate applications in mutual recognition and decentralised procedures’ and to Volume 2A, Chapter 2 of the Notice to Applicants.

5.1.2 Conditions relating to the duplex medicinal product

The dossier for the duplex medicinal product must be identical to that of the reference product at the time of submission of the application for the duplex marketing authorisation. The following points and their associated documents in Module I (see section 5.2) are exceptions:

a. the RVG number
b. the product name
c. the marketing authorisation holder
d. the person responsible for communication on behalf of the marketing authorisation holder
e. the person responsible for pharmacovigilance
f. the summary of the Pharmacovigilance System Master File (PSMF)
g. layout of the mock-up and package leaflet

For more information, please refer to section 5.2 of this policy document.

The MEB only accepts electronic submissions that meet the eCTD (Electronic Common Technical Document) standard and the Nees (Non eCTD electronic Submission) specifications. Information about these standards and other relevant information about electronic submissions can be found on the website of the MEB[1] and on the European eSubmission website of the EMA (European Medicines Agency)[2].

An integrated version of the duplex dossier must be submitted for the duplex application (a so- called baseline version).

5.2 Documents to be provided

The following documentation must be enclosed with the request in order to be considered for marketing authorisation.

1. Module 1, including:
    a) a signed accompanying letter;
    b) applicable model declarations I and II, complete and filled in and signed;
    c) a complete and filled in and signed application form for authorisation of medicinal products in module 1.2 (Notice to Applicants), including:
        i. Annex 5.3: evidence that the marketing authorisation holder resides in the EEA;
        ii. Annex 5.4: Power of Attorney (this is only required if the person responsible for communication does not work for the future marketing authorisation holder);
        iii. Annex 5.6 and 5.9: valid manufacturing authorisation and/or valid GMP certificate for all manufacturers referred to in the application form that are responsible for final production, batch control/testing, packaging and/or release;
        iv. Annex 5.8: flow chart of all manufacturers involved;
        v. Appendix 5.10: a CEP or, if an ASMF is used, a Letter of Access (in the name of the duplex holder);
        vi. Annex 5.11: confirmation from the manufacturer of the active ingredient that the marketing authorisation holder is to be informed in the event of changes to the manufacturing process or the specifications in accordance with Annex I of Directive 2001/83/EC;

[1] https://english.cbg-meb.nl/topics/mah-technical-validation
[2] http://esubmission.ema.europa.eu/esubmission.html

   vii. Annex 5.22: valid GMP declaration(s) for the manufacturer(s) of the active ingredient or the active ingredients;
d) SmPC, package leaflet and labelling, both as pdf file (module 1.3.1) and in Word (working documents);
e) package leaflet for the professional medical users, if present for the reference product, both as pdf file (module 1.3.1.) and in Word (working documents);
f) educational material, if present for the reference product, both as pdf file and in Word (working documents);
g) declaration of technical readability for a duplex marketing authorisation;
h) mock-up(s) or a declaration that the product will not be marketed immediately and that the mock-ups still have to be submitted for approval by the MEB before the product is marketed (module 1.3.2);
i) a braille declaration (module 1.3.6);
j) a summary of the Pharmacovigilance System Master File (PSMF) of the duplex applicant (module 1.8.1);
k) the Environmental Risk Assessment (ERA) (module 1.6).
l) the Risk Management Plan (RMP) (module 1.8.2).

2. Modules 2 and 3.
3. Modules 4 and 5, if these are also present in the reference dossier.

Ad 1.a en 1.c: If CESP (the portal) is used, an original signature is not required in the cover letter and the application form.

Ad 1.b: The templates for the current model declarations I and II can be found on the MEB website..

Ad 1.c iii: For more information please refer to the MEB web page entitled ‘Site clearance’.

Ad 1.c vi: There must be a GMP declaration for each clearance and final product manufacturer located in the EEA and listed in the application form. It is also permitted to have a single GMP declaration on behalf of all clearance and final product manufacturers. For more information, please refer to the ‘Site clearance (MEB 30)’ document and to the MEB web page ‘Site clearance’.

Ad 1.d en 1.e: For more information, please refer to section 5.5 of this policy document.

Ad 1.i: A full, completed and signed Braille declaration must be submitted for the duplex medicinal product. However, this does not apply to products that are only administered by healthcare professionals. Please refer to the MEB website for the template for the declaration and for the EU directives regarding Braille.

Ad 1.k: The ERA must be identical to the ERA of the reference product, (except for product-specific characteristics such as the product name). If the ERA of the reference product does not comply with the ERA guideline that came into force on 1 September 2024, before the duplex application can be submitted, the dossier of the reference product must first be aligned with this ERA guideline through a variation. Until 31 May 2025, a commitment that the ERA will be aligned with the new ERA guideline will be accepted. For a duplex with additional conditions, the commitment must be issued by the marketing authorisation holder of the reference product.

Ad 1.l: The RMP must be equal to the RMP for the reference product, with the exception of those sections related to the marketing authorisation holder.

Ad 2 en 3: The dossier modules 2 through 5 must be identical to those of the reference product.

If one or more of the above-mentioned dossier documents are missing or not complete, the applicant will be asked to send the missing documentation and a clock-stop will be implemented for the application procedure. The processing of the application will resume upon receipt of the missing documentation.

5.3 Nomenclature of duplex medicinal product

The name of the duplex medicinal product must meet the current requirements regarding nomenclature of pharmaceutical products for human use. The product name can be the same as that of the reference product (provided this name meets the current nomenclature requirements).

For more information, please refer to the ‘Nomenclature of pharmaceutical products (MEB 13)’ policy document.

5.4 Ongoing dossier variations for the reference product

At the time of submission of the application for a duplex marketing authorisation, the duplex dossier must be identical to the dossier for the reference product approved at that time. This means the following:

If a variation for the reference dossier is approved (just) before submission of the duplex application, then the variation must first be incorporated in the duplex dossier before the duplex application is submitted. However, if a variation is ongoing at the time of submission of the duplex application (and the variation has therefore not yet been approved by the MEB), or such a variation will be implemented for the reference product dossier during the processing of the duplex application, then this variation does not have to be included in the

duplex dossier in order to be eligible for a marketing authorisation.

If the ongoing procedure for the reference product (whether directed by the MEB or not) was submitted in order to continue to meet the admission requirements, then a clock-stop will be implemented for the application for the duplex marketing authorisation until the procedure for the reference product has been completed. The duplex dossier must be updated upon completion of the procedure.

5.5 Product information

5.5.1 Requirements for the product information

The product information (SmPC, package leaflet and labelling) must be identical (verbatim) to that of the reference product, with the exception of:

- the product name
- the name and address of the marketing authorisation holder
- the RVG number
- the date of first authorisation/renewal of the authorisation

If the reference product has a combined SmPC and/or package leaflet and a duplex marketing authorisation application is being submitted for only some of the included RVG numbers, then the section on dosage instructions must be reviewed in both the SmPC and the package leaflet for the duplex medicinal product.

If a dosage recommendation cannot be performed using the duplex medicinal product (or the duplex medicinal products), then all indications must be checked to determine whether they are still feasible. If this is not the case, the indication that cannot be used and all information related to this indication must be removed from the SmPC and the package leaflet. However, if all indications can still be used but not the entire dosage recommendation for each indication, one of the following Dutch sentences must then be added depending on the situation in this section of the SmPC and the package leaflet:
"*De aanbevolen doseringen zijn niet allemaal mogelijk met dit product, er zijn echter ook producten met een lagere sterkte dan <sterkte duplexgeneesmiddel> beschikbaar*", of
"*De aanbevolen doseringen zijn mogelijk met dit product. Er zijn echter ook producten met een hogere sterkte dan <sterkte duplexgeneesmiddel> beschikbaar, waardoor minder <tabletten><capsules><etc.> per keer nodig zijn*".

Meaning:
"*The recommended doses are not all possible using this product, however, products with dosage lower than <strength of duplex medicinal product> are available*", or
"The recommended dosages are possible for this product. However, there are also products available with a higher dose than <strength of duplex medicinal product>, so fewer <tablets><capsules><etc.> will be required per time".

A full, completed and signed duplex package leaflet declaration must be submitted for the layout of the package leaflet. This declaration can be found on the MEB website.

The mock-ups must meet the regulations in the 'Labelling of pharmaceutical products (MEB 6)' policy.

5.5.2 The reference product has a marketing authorisation with further conditions

For a product with a marketing authorisation with further conditions, no Dutch translation of the product information has been determined; in such cases, the (English) 'common' product information takes precedence. If a duplex marketing authorisation application is submitted for a reference product that is authorised under further conditions, then the duplex will also be authorised under further conditions. After the marketing authorisation has been issued, a national 61(3) notification can be submitted in order to have Dutch translations of the 'common' product information approved. This notification must be provided at least two months before marketing the product.

5.5.3 Package leaflet for medical professionals

If the reference product includes a package leaflet for medical professionals, then this information must also be included for the duplex dossier. The text must be identical (verbatim) to the package leaflet for medical professionals for the reference product.

5.5.4 Educational material

For some products, there are additional requirements regarding information for the user and/or healthcare practitioner, known as the educational material (aRMM). An example of this is the patient card. It includes important instructions for use of the product. If this educational material is available for the reference product, then this must also be submitted for the duplex medicinal product. This educational material must be in Dutch. The text must be identical (verbatim) to the text for the reference product.

The aRMM for duplex medicinal products is not actively distributed by default, but there are exceptions. The MEB will determine, during the assessment of the duplex application, whether active distribution is required and - if so - to which target groups.

5.6 PSUR cycle

If the active ingredient or the active ingredients is/are not included on the EURD list, then the PSUR cycle for the reference product must be followed.

6. Maintenance of the dossier after marketing authorisation has been granted

The duplex application will result in a "normal" marketing authorisation. One of the requirements is that the dossier will continuously be kept up-to-date by the marketing authorisation holder once the marketing authorisation has been granted.

Once the marketing authorisation has been granted, the marketing authorisation holder has the option to implement variations according to prescribed procedures, irrespective of the reference dossier. The authorised duplex medicinal product effectively has a stand-alone dossier.

As with an ordinary national marketing authorisation, a mutual recognition procedure (MRP) for a duplex marketing authorisation cannot be started at random. An MRP can only be started after it has been determined that the dossier meets all the dossier requirements that are applicable at that time for new applications.

7. Duplex with supplementary conditions

If the reference product was registered more than five years ago, it is possible to register a duplex. However, the following supplementary conditions apply in addition to the conditions described under §5.1:

a. the dossier for the duplex medicinal product will remain identical to the dossier for the reference product after granting the marketing authorisation;
b. an MRP cannot be started with this duplex medicinal product;
c. if the marketing authorisation for the reference product is withdrawn at the request of the authorisation holder, then a request for withdrawal of the marketing authorisation for the duplex medicinal product must be submitted within 3 months.

Contrary to a normal duplex medicinal product, this duplex medicinal product with supplementary conditions does not result in a stand-alone marketing authorisation for which variations can be submitted that have not been submitted for the reference product. This duplex medicinal product remains linked to the reference product.
In order to characterise this duplex as such, this duplex medicinal product is assigned a double RVG number in the form of RVG1=RVG2, where RVG2 is the number of the reference product.

If a variation has been submitted and completed for the reference product, then this same variation must be submitted for the duplex medicinal product within 2 months of the

approval. The variation for the duplex medicinal product must consist of a consolidated dossier (all rounds of the variation procedure for the reference product combined) together with a declaration that it is identical to the variation that has already been approved for the reference product.

Separate model declarations apply to this duplex procedure (available on the MEB website).

The marketing authorisation of a duplex with supplementary conditions can be transferred to another (legal) entity. In addition to the usual information to be provided (see Question and answer document concerning not covered by the Variation Regulation 1234/2008), the following must also be submitted:

1. A statement from the new marketing authorisation holder of the duplex that the supplementary conditions are being adopted;
2. A statement from the marketing authorisation holder of the reference product that they agree with the transfer;
3. A statement from the marketing authorisation holder of the reference product that the new marketing authorisation holder of the duplex will be kept informed of any changes in the dossier of the reference product; in the sense that within 1 month after approval of a change in the dossier of the reference product, the changed dossier parts will be made available to the new marketing authorisation holder of the duplex;
4. A statement from the marketing authorisation holder of the reference product that the new marketing authorisation holder of the duplex will be informed if a request for withdrawal of the marketing authorisation of the reference product has been submitted to the MEB.

8. Related documents

1. Duplex declarations normal.
2. Duplex declarations with supplementary conditions.
3. Declaration of technical readability for a duplex authorisation.