Policy document MEB 48

The national informed consent request

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2 Abbreviations and definitions

ASMF	Active Substance Master File
MEB	Medicines Evaluation Board
CEP	Certificate of Suitability
CESP	Common European Submission Portal
CMS	Concerned Member State
DC	Decentralised
DCP	Decentralised Recognition Procedure
eCTD	Electronic Common Technical document
EEA	European Economic Area
EMA	European Medicines Agency
EURD list	European Union reference dates
GMP	Good Manufacturing Practice
LoA	Letter of Access
MR	Mutual Recognition
MRP	Mutual Recognition Procedure
NtA	Notice to Applicants
PoA	Power of Attorney
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RMS	Reference Member State
RVG	Register Packaged Medicinal Products
SmPC	Summary of Product Characteristics

3 Introduction

An Article 10c “Informed Consent” request is an authorisation application based on the full reference to the dossier of another product (=the reference product), with the consent/authorisation of the marketing authorisation holder of that reference product. The applicant can in this case be the same as the marketing authorisation holder of the reference product, or it can also be another applicant.

In an “informed consent” procedure, the company effectively makes a copy of an existing authorisation dossier, with the exception of the legal underpinnings. An “informed consent” product has its own legal basis (10.c).

4 Purpose and scope

The key requirement for an informed consent request is that the company takes over the complete dossier of the reference product (or can inspect it at all times) and that it has been given permission to

do so by the marketing authorisation holder of the reference product. An Article 10c “Informed Consent” application can therefore only be made for a product that is identical except for the administrative data (module 1). It is therefore not possible to choose Article 10c as the legal basis for an application that consists of the applicant's own module 3, but for which permission has been given for modules 4 and 5.

An informed consent application procedure will remain limited to an administrative procedure, provided that the reference product has not been authorised more than five years ago. The marketing authorisation will then be issued within 45 days. These 45 days are excluding any clock-stop period. The informed consent applicant only has to submit module 1 for this. After authorisation, the informed consent authorisation will remain the same as the reference product, and the same variations will have to be submitted as for the reference product. However, if the informed consent applicant also has the reference dossier, it may choose to submit the complete dossier to the MEB. After authorisation, the informed consent authorisation can be absolute: the informed consent marketing authorisation holder can then make changes to the dossier using the procedures prescribed, independently of the reference dossier.

An informed consent application can also be made for which the reference product was authorised more than 5 years ago. However, the content of the application dossier will now be evaluated in order to guarantee that the dossier for which the informed consent marketing authorisation was issued meets the applicable dossier requirements for new authorisations. In this situation, the application procedure will take a maximum of 210 days and a higher rate will be applicable. The complete dossier will also have to be submitted by the applicant for evaluation in this situation. This situation is therefore only possible if the applicant physically possesses the dossier and not if the dossier is merely available for ‘inspection’.

Just like a normal national marketing authorisation, a mutual recognition procedure (MRP) for an informed consent marketing authorisation can only be started after it has been determined that the dossier complies with all the dossier requirements applicable to new requests at that moment.

In order to be considered for a marketing authorisation, both the informed consent product and the reference product must meet certain conditions. Specific documentation must also be submitted. For more information please refer to chapters 2 and 3 of this policy document.

In the following chapters, the product for which the informed consent marketing authorisation is requested will be referred to as the “informed consent medicinal product” or “product A”, and the informed consent applicant (the future authorisation holder) as “(legal) entity A”. A medicinal product that is already authorised is referred to as the “reference product” or “product B”, and the authorisation holder of that product as “(legal) entity B”.

5 Procedure/Assessment criteria

5.1 Conditions regarding the informed consent and reference product.

In order to be considered for an informed consent marketing authorisation, the informed consent medicinal product must meet the conditions summarised in Section 2.1.2, while the medicinal product that the informed consent marketing authorisation is based on must meet the conditions summarised in Section 2.1.1.
If one or more of the conditions stated below are not met, the MEB will neither validate nor handle the application. The procedure will only be started after the validation issues have been resolved.

5.1.1 Conditions regarding the reference product

1. No marketing authorisation has been issued for the reference product through the centralised procedure.
2. No marketing authorisation has been issued for the reference product through the duplex procedure.
3. No marketing authorisation has been issued for the reference product through the informed consent procedure.
4. The reference product has a valid marketing authorisation which has been issued through the national procedure or DC/MR procedure.
5. The reference product is either related to an authorisation based on a complete dossier, or the legal basis of the reference product is 8(3), 10(a) or 10(b). The marketing authorisation for the reference product must not be based on an application pursuant to articles 10(1), 10(3) or 10(c).
6. The legal basis of the reference product is known and has been recorded by the MEB.
7. If the reference product is an NL=CMS authorisation, legal entities A and B must be neither the same nor be related to each other.
8. The reference product has an approved Risk Management Plan (RMP).

Point 1: If the reference product has been authorised through the centralised procedure, the informed consent application will have to be submitted to the EMA.

Point 2: If the reference product has been authorised through the duplex procedure, it is possible that the original underlying file that the authorisation is based on may be more than five years old. Even if the reference product of the informed consent application was authorised less than five years ago, the informed consent request is still actually based on a dossier that was fully evaluated more than five years ago.

Point 3: If the reference product has been authorised through the informed consent procedure, it is possible that the original dossier that the authorisation is based on will be more than five years old. Even if the reference dossier of the current informed consent application was authorised less than five years ago, the informed consent application is still actually based on a dossier that was fully evaluated more than five years ago.

Point 7: The condition that the reference product must not have been authorised through the DCP or MRP (where NL=CMS) applies when the marketing authorisation holder of the reference product and the informed consent applicant are the same (legal) entities or related to each other.

- A CMS is legally not permitted to recognise the marketing authorisation issued by the RMS more than once. A copy application for a dossier by the same marketing authorisation holder must therefore always be submitted to the country where the authorisation was first awarded (RMS). This means that the informed consent procedure cannot be performed if the original marketing authorisation was issued in any country other than the Netherlands first. An exception applies if the authorisation holder of the reference product is not the same as the informed consent applicant: the informed consent procedure can then be carried out.
- As mentioned in the Commission Communication No. 98C 229/03, companies are considered to be the same entity if they belong to the same mother company or group of mother companies, or if '*concluded agreements' (e.g. "licensees")* or '*concerted practices*' exist for the marketing of medicinal products. The fact that any form of cooperation between two companies exists in the context of an informed consent application does not justify in itself the conclusion that a 'concerted practice' is involved (see the ruling of the Council of State in the appeal by

GlaxoSmithKline BV against the verdict of the Utrecht court on 15 May 2003 (dated 21 July 2004)).

For more information, please refer to the CMDh document "Recommendations on multiple/duplicate applications in mutual recognition and decentralised procedures" and to Volume 2A, section 2, of the Notice to Applicants.

5.1.2 Conditions regarding the informed consent medicinal product

The dossier of the informed consent medicinal product must be the same as that of the reference product at the moment of submission of the application for the informed consent marketing authorisation. Exempted are the following items and associated documents in Module I (refer to §2.2):

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. lay-out of the mock-up and package leaflet

For more information, please refer to section 2.2 of this policy document.

The MEB will only accept electronic submissions that meet the eCTD standard. Information about these standards and other relevant information about electronic submissions can be found on the MEB website, as well as the European eSubmission website of the EMA.

5.2 Documentation to be submitted

The following documentation must accompany the application in order to be eligible for a marketing authorisation:

1. Module 1, including:
   a) a signed accompanying letter. The accompanying letter must state what the reference product is and when it was authorised. It must also state whether a stand-alone authorisation is intended (in that case, the complete dossier has to be submitted, not just Module I).

   b) applicable informed consent declaration templates I and II, fully completed and signed. The declaration templates comprise:

      i. A declaration by the marketing authorisation holder of the reference dossier stating that the informed consent applicant is in possession of the reference dossier, or that it has permission to refer to modules 2, 3, 4 and 5 of the reference product and also to all the new documentation that will be added to the reference dossier.
      ii. A declaration by the applicant confirming that it has access to or is in possession of the reference dossier, and that modules 2, 3, 4 and 5 are therefore identical to the reference product.

      iii. If the informed consent applicant has only submitted module 1, the following declarations must be made:

by the informed consent applicant:

- that a letter of authorisation will be submitted by the new marketing authorisation holder of the reference product if the reference product authorisation holder changes, or, if the latter does not wish to give access to the reference dossier, that a request for withdrawal of the marketing authorisation for the informed consent product will be submitted.
- if the marketing authorisation for the reference product is withdrawn, the marketing authorisation for the informed consent product will be withdrawn too, unless the informed consent applicant actually will have or has the reference dossier and will submit this dossier to the MEB.

by the marketing authorisation holder of the reference product:

- that if the marketing authorisation holder of the reference dossier submits a variation, a variation for the informed consent product will also be submitted at the same time.

c) a fully completed and signed application form for in module 1.2 (Notice to Applicants), including:
   i. Annex 5.3: evidence that the marketing authorisation holder resides in the EER;
   ii. Annex 5.4: Power of attorney (this is only necessary, if the person responsible for communication is not employed by the future marketing authorisation holder);
   iii. Annexes 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 involved manufacturers;
   v. Annex 5.10: a CEP or, if an ASMF is used, a Letter of Access (in the name of the informed consent 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;
   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 text(s), both as PDF file (module 1.3.1) and in Word (working documents);
e) package leaflet for professional medical users, if present for the reference product, both as a PDF file (module 1.3.1.) and in Word (working documents);
f) educational material, if present for the reference product, both as a PDF file and in Word (working documents);
g) technical readability declaration for an informed consent marketing authorisation;
h) mock-up(s) or a declaration that the product will not be marketed immediately and that the mock-ups will be submitted to the MEB for approval 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 informed consent applicant (module 1.8.1);
k) the risk management plan (RMP) (module 1.8.2).

If the reference product was authorised less than five years ago, only module 1 must be submitted (together with the above-mentioned documents). However, if the informed consent applicant wishes to make changes to the dossier after authorisation, independently of the reference dossier, the complete dossier must be submitted (modules 1 through 5). This is therefore only possible if the applicant is in possession of the reference dossier.

Points 1.a and 1.c: If using CESP (portal), an original signature is not required for the cover letter and application form.

Point 1.b: The templates for the applicable informed consent declarations (templates I and II) can be found on the MEB website.

Point 1.c iii: For more information, please refer to the MEB website: Site clearance.

Point 1.c vi: A GMP declaration must be present for every release manufacturer or final manufacturer located in the EEA and listed on the application form. A single GMP declaration on behalf of all release manufacturers and final manufacturers is also permitted. For more information, please refer to the MEB website: Site clearance.

Points 1.d and 1.e: For more information, please refer to section 5 of this policy document.

Point 1.i: A fully completed and signed declaration in Braille must be provided for the informed consent medicinal product. However, this does not apply to products that will be administered exclusively by medical professionals. Please refer to the MEB website for the template for the declaration and for the EU directives regarding Braille.

Point 1.k: The RMP must be the same as the RMP of the reference product, except for those parts that are associated with the authorisation holder.

If one or more of the dossier modules described above is/are not present or not complete, then the applicant will be asked to submit 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 the informed consent medicinal product

The name of the informed consent medicinal product must meet the applicable requirements regarding the nomenclature of pharmaceutical products for human use. For more information, please refer to the policy document "Nomenclature of pharmaceutical products" (MEB 13)".

5.4 Dossier changes for the reference product

When submitting the application for an informed consent marketing authorisation, the informed consent dossier must be identical to the approved dossier of the reference product at that moment. This means that if a variation for the reference dossier is approved (just) before submitting the informed consent request, this variation has to be processed in the informed consent dossier first before the informed consent application is submitted.
If at the time of submitting the informed consent application a variation is being processed for the reference product (and the variation has therefore not yet been approved by the MEB), or if such a variation will be processed while the informed consent application is being handled, this variation does not have to be included in the informed consent dossier in order for it to be considered for marketing authorisation. However, this only applies if the informed consent applicant has the complete dossier in its possession and has submitted it in full. In the alternative situation where the informed consent applicant has only submitted module I, this module will only be handled after the variations for the reference dossier have been dealt with.

If the current procedure for the reference product has been submitted (whether or not by order of the MEB) in order to continue to meet the authorisation conditions (withdrawal, suspension or change), the application for the informed consent marketing authorisation will be halted until the procedure for the reference product has been completed. The informed consent dossier must be updated after completion.

5.5 Product Information

5.5.1 Requirements related to the product information

The product information (SmPC, package leaflet and labelling) must be the same, word for word, as that of the reference product, with the exception of:

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

If there is a combined SmPC and/or package leaflet for the reference product and if an informed consent marketing authorisation is not being requested for all the RVG numbers included in this, the section with dosage instructions must be checked in both the SmPC and the package leaflet for the informed consent medicinal product. If a dosage recommendation cannot be used for the informed consent medicinal product, checks must be made to determine whether all the indications can still be used. If this is not the case, then the indication that is not feasible - and all related information - must be removed from the SmPC and package leaflet. If all indications are still feasible, but the full dosage recommendation for each indication is no longer feasible, then - depending on the situation - one of the following sentences must be added to this section in the SmPC and package leaflet:

- "*Not all of the recommended dosages are possible for this product; however, there are also products available with a lower strength than <strength of informed consent medicinal product>*",

  or

- "*The recommended doses are possible with this product. "However, there are also products available with a higher strength than <strength of informed consent medicinal product>, which therefore require fewer<tablets><capsules><etc.> at a time*".

In Dutch:

- "*De aanbevolen doseringen zijn niet allemaal mogelijk met dit product, er zijn echter ook producten met een lagere sterkte dan <sterkte informed consent geneesmiddel> beschikbaar*",

  of

- "*De aanbevolen doseringen zijn mogelijk met dit product. Er zijn echter ook producten met een hogere sterkte dan <sterkte informed consent geneesmiddel> beschikbaar, waardoor minder <tabletten><capsules><etc.> per keer nodig zijn*".

A fully completed and signed package leaflet declaration ('Declaration regarding the technical aspects of the readability of the package leaflet for pharmaceutical products for human use') must be enclosed for the layout of the package leaflet. This declaration is available on the MEB website.

The mock-ups must meet the requirements listed in the policy document "Labelling of pharmaceutical products (MEB 6)".

5.5.2 The reference product has been authorised subject to further conditions

For a product that is registered under further conditions no Dutch translation of the product information has been approved; the (English) "common" product information takes precedence in that case. If informed consent marketing authorisation is requested for a reference product that has been authorised subject to further conditions, the informed consent application must also be authorised subject to further conditions. Once the marketing authorisation has been awarded, a national 61(3) notification can be submitted for approval of Dutch translations of the "common" product information. This notification must be submitted at least two months prior to the marketing of the product.

5.5.3 Package leaflet for professional medical users

If a package leaflet for professional medical users has been determined for the reference product, this leaflet should also be included in the informed consent dossier. The text must be the same, word for word, as the text in the package leaflet for professional medical users of the reference product.

5.5.4 Educational material

For some products, there are additional requirements regarding information for the user and/or medical professionals, the so-called educational material or information material. An example of this is the patient card. This card contains important instructions for use
of the product. If there is such educational material for the reference product, these must also be submitted for the informed consent medicinal product. This educational material must be drafted in Dutch. The text must be literally the same as the text for the reference product.

When evaluating the informed consent application, the MEB will determine what kind of distribution will be required and if so, among which target groups.

5.6 PSUR cycle

The PSUR cycle of the reference product must be followed if the active ingredient or ingredients has or have not been included in the EURD list.

6 Maintenance of the dossier following awarding of the marketing authorisation

Informed consent authorisation for which only module 1 had been submitted is not a stand-alone authorisation. If a variation for the reference product is submitted, this variation must also be submitted for the informed consent authorisation at the same time (see also the template declarations).
It is not possible to make changes to the informed consent dossier if these changes are not implemented for the reference product too (with the exception of the dossier elements stated in Section 2.1.2).

If the new informed consent holder is in possession of the complete reference dossier and has submitted it in full to the MEB at the time of the application, the informed consent will be considered a stand-alone authorisation. This means that, after marketing authorisation has been granted, the marketing authorisation holder can make changes to the dossier, using the procedures prescribed for this, independently of the reference dossier.

As in the case of a standard national marketing authorisation, a mutual recognition procedure (MRP) cannot be started outright for a medicinal product that has been authorised using an informed consent procedure. An MRP can only be started once it has been confirmed that the dossier meets all the current dossier requirements for new applications.