CBG MEB

MEDICINES EVALUATION BOARD

Policy Document

Parallel importation: marketing authorisation and maintenance

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1. New applications

1.1 Introduction

The parallel importation of medicinal products is the importation and subsequent marketing in the Netherlands of a medicinal product that has been authorised elsewhere in the EU by an importer who has not been appointed by the original authorisation holder, whilst an identical or virtually identical version of this medicinal product is already authorised in the Netherlands, the so-called Dutch reference product.

An application for awarding a parallel marketing authorisation is processed in accordance with Article 48 of the Medicines Act and according to the policy set out in this document.

A parallel marketing authorisation is valid for the same indications, contra-indications, adverse reactions, dosage and method of use and administration as for the reference medicinal product (Article 48, section 2, of the Medicines Act). At the time of applying for the parallel product, the Dutch reference product must have a valid marketing authorisation.

The MEB will assess whether the product for parallel importation does not differ from the Dutch reference product in terms of safety and efficacy and whether these products are interchangeable (the products are identical/virtually identical). During the assessment of an application for awarding a parallel marketing authorisation, the starting point is that the product already has a valid marketing authorisation elsewhere in the EU and that trade barriers may not be created, unless there is a risk to public health.

1.2 Assessment criteria parallel application

1.2.1 Interchangeability/identical - virtually identical

A. General

The assessment will determine whether the product for parallel importation does not differ from the reference product as far as safety and efficacy are concerned; the parallel product must be **interchangeable** or **identical or virtually identical** to the reference product (Art. 48, section 1, of the Medicines Act). The following assessment criteria are important in this case:

- A reference product that is authorised in the Netherlands must be designated. This reference product must have a valid marketing authorisation at the time of submission of the application for the parallel importation product (see §1.2.5).
- The dosage to be administered must be identical or virtually identical (see §1.2.1-B and §1.3.11-B).
- The qualitative and quantitative composition of the active ingredient or active ingredients of the product for parallel importation must be equal to those of the reference product.

- The qualitative composition of the excipients must be identical or virtually identical. In the case of products with a local effect or products with controlled release, this requirement also applies to the quantitative composition. An exception to these conditions can only be made if it can be assumed that the difference in excipients does not have any effect on the interchangeability (see §1.2.1-C).
- The pharmaceutical form of the parallel importation product must be identical to that of the reference product. The various oral immediate release forms are viewed as the same pharmaceutical form in this case.
- The method of administration, preparation and supplied devices (including dosage accuracy) must be equal to those of the Dutch reference product. A difference is only acceptable if it can be assumed that this will not result in possible incorrect use and subsequent risk to public health (see §1.2.1-D).
- The storage conditions of the parallel importation product (before and after opening, after further preparation) and - if relevant - the shelf life after being brought into use, as approved in the country of origin must be equal to those of the Dutch reference product. A difference in storage conditions and/or storage period compared to those approved for the reference product is only acceptable if it is not expected to result in problems with use and subsequent risk to public health (see §1.2.1-E).
- The package size to be imported should be identical or virtually identical to the packaging approved for the Dutch reference product. A difference in package size is only acceptable if this falls within the same legal status of supply and if the same dosage schedule (treatment duration) can be followed as has been approved for the Dutch reference product (see §1.2.1-F). In addition, different package sizes also have to have the same origin. An additional package size, which falls under a different marketing authorisation, or comes from a different member state, must be submitted as a new application and will be fully assessed.

B. Difference in (function of) a break line

If there is a difference between (the function of) a break line of the parallel product and the Dutch reference product, it may be that the dosage instruction is not entirely feasible. If the difference concerns the function (to divide the tablet into equal halves/to make it easier to break the tablet) or absence of a break line in the parallel product, the parallel applicant has to argue that the parallel product is identical or virtually identical to the Dutch reference product. An assessment must also be made to determine whether the entire dosage instruction and whether all indications can be executed. If a break line has been added for the parallel product while this is missing from the Dutch reference product, one must check whether the foreign package leaflet includes information about the function of the break line. If so, this information must be included in the Dutch package leaflet for the parallel product.

C. Difference in excipients

As far as excipients are concerned, the composition of a parallel product and the Dutch reference product should be virtually identical in this case. In the case of products with a local effect and products with controlled release, even a quantitative difference in

excipients can result in differences in biological availability and subsequent differences in efficacy and/or safety.

A difference in excipients is only acceptable if this does not result in a difference in safety and/or efficacy.

D. Difference in method of administration and/or preparation

If the method of administration - e.g. due to a difference in (the dosage accuracy of) supplied devices - and/or preparation of the parallel product (this also includes a difference in compatibility with various solvents/dilutants or a difference in final concentration (range)) - differs from that of the Dutch reference product, this can endanger the patient's safety. There is a risk that the medical professional or the user is not used to/familiar with the method of preparation and/or administration of the parallel product, which could result in incorrect use. The parallel application cannot be accepted in such cases.

See also §1.2.2 and §1.3.6. and §1.3.8.

E. Difference in storage conditions and shelf life after being brought into use

The parallel importation product must be kept under the storage conditions approved by the authorisation authority in the country of origin. This relates both to the storage conditions for opening and the storage conditions that apply after being brought into use (after opening and - if relevant - further preparation). The parallel importation product must be kept under the storage conditions after being brought into use, as approved by the country of origin, if such a period has been defined. The reason for this is that the authorisation authority in the country of origin has used the data in the dossier to stipulate the conditions that guarantee the quality of the product.

Storage conditions and, if relevant, shelf life after being brought into use of the parallel importation product can sometimes differ (slightly) compared to those of the Dutch reference product. If the difference is such that switching from the Dutch reference product to the parallel product or vice versa in daily practice could result in errors in storage that could result in a risk to the user, the parallel application cannot be accepted.

If a difference in storage conditions exists, the comparison form (see §1.3.4) must be used to argue whether or not this can result in a risk to the user.

If the Dutch reference product has more stringent storage conditions, it is not the intention that these are adopted for the parallel importation product.

In the case of OTC medicinal products the shelf life and storage conditions after opening should *always* be stated. See also MEB 6.

F. Package size and legal status of supply

The package size of medicinal products should be identical or virtually identical to the packaging approved for the Dutch reference product. If this is not the case, the MEB will

assess whether the package size matches the treatment duration as stated in the SmPC of the reference product. The MEB also assesses whether the package sizes that are to be imported fall within the canalisation of the reference product. The package size can determine whether a product is awarded the PH, PDO or GS status. The package size that will be imported must fall under the same legal status of supply as has been approved for the reference product. If this is not the case and/or the treatment duration approved for the reference product cannot be performed with the package size that is to be imported, the parallel application cannot be accepted. In addition, different package sizes also have to have the same origin. An additional package size, which falls under a different marketing authorisation, or comes from a different member state, must be submitted as a new application and will be fully assessed.

Also refer to §1.2.2.

1.2.2 Change in packaging contents

The contents of the packaging (e.g. a device) of the product for parallel importation may only be adapted if this adaptation is essential to ensure that the parallel product is identical or virtually identical to the reference product, e.g. in order to negate a difference in use. A proposal for adaptation of the contents of the packaging must be clearly described and substantiated in the application for a parallel marketing authorisation. It is up to the MEB to determine whether the change in the contents of the packaging will result in both products being identical/virtually identical and whether this is acceptable. If necessary, the MEB will also assess any additional items for e.g. quality. The parallel applicant must submit additional data for this assessment. Also refer to §1.3.8.

The adaptation of the packaging size is subject to the conditions described in §1.3.15-B).

1.2.3 Product is a medical device in the country of origin

If the product for parallel importation is not authorised as a medicinal product in the country of origin, but as a medical device (as denoted by a CE marking on the packaging), the application is not acceptable. The quality requirements for medicinal products are more stringent than for medical devices. Furthermore, medical devices are not assessed by an authorisation authority for medicinal products - such as the MEB - but by a Notified Body. As a result, the dossier does not meet the requirement of Directive 2001/83/EC. Legal entities intending to import a medical device should contact the relevant authority about this.

1.2.4 Parallel importation of a product from a European sister company

The authorisation holder of the product for parallel importation in the country of origin may not be the same company and may not be affiliated[1] to the legal entity that intends to

[1] As stated 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.

market the product in the Netherlands (the importer / future parallel marketing authorisation holder). The parallel importation is not permitted if they are the same entity or are affiliated. The Mutual Recognition Procedure (MRP) should be followed instead. Please refer to the HMA website for more information about MRP.

An exception to this will be made if the parallel importation of an “own” medicinal product will take place. In other words, the importer for the product that is to be imported is already in possession of a valid marketing authorisation in both the country of export and the country of import. In that case the importer in the Netherlands has two authorisations for the same product, a “normal” marketing authorisation and a parallel marketing authorisation.

1.2.5 Ongoing suspension or withdrawal of authorisation or GMP/GCP problem for Dutch reference product

If the MEB intends to suspend or withdraw the marketing authorisation of the Dutch reference product due to problems regarding the efficacy, safety or quality, the MEB will place a clock-stop on the parallel application until a decision has been made regarding the suspension or withdrawal. The parallel application cannot be accepted if the suspension or withdrawal is enforced.

If there is a report pending for the Dutch reference product in relation to the GMP or GCP status and this applies or could also apply to the parallel product, the parallel application cannot be accepted before the GMP or GCP problem is resolved.

1.3. Data and documentation to be submitted

1.3.1 Introduction

A. Documentation

This must demonstrate that the parallel product is identical or virtually identical to the Dutch reference product. The applicant must submit the following documents to underpin the parallel application:

1. Application letter (§1.3.2)
2. Application for awarding of a parallel marketing authorisation (§1.3.3)
3. Comparison form (§1.3.4)
4. Comparison photo (cover) of the parallel product and the Dutch reference product and of any included medical device (§1.3.5)
5. Photograph (colour) of all sides of the foreign inner and outer packaging (§1.3.5)
6. Foreign package leaflet
7. Proposed package leaflet for the parallel product (Word file) (§1.3.11)
8. Package leaflet declaration (§1.3.11)
9. Proposed label text (Word file) or new outer packaging (PDF file) (§1.3.15)
10. Manufacturing authorisation, with or without wholesale distribution authorisation, or parallel wholesale distribution authorisation: copy of EudraGMP reference (§1.3.17)

Depending on the situation, the following documentation may also be needed:

11. Authorised translation of (parts of) the foreign package leaflet (§1.3.13)
12. Proof that the parallel product and the Dutch reference product have completed the same MRP/DCP (§1.3.4)
13. Declaration from Member State of origin of the parallel importation + copy of notification to the patent holder, or a declaration that the parallel product is no longer subject to patents or additional protection certificate (§1.3.18)
14. Package leaflet for the medical professionals (§1.3.12)
15. Declaration regarding the package leaflet for the medical professionals (§1.3.12)
16. Extra educational material and a declaration that the material is and will remain literally the same as that of the Dutch reference product (§1.3.16)
17. Declaration about making certain information invisible on the foreign packaging (§1.3.15)
18. Foreign SmPC (§1.3.6)
19. Authorised translation of parts of the foreign SmPC (§1.3.6 and §1.3.13)
20. Additional data to underpin that the parallel product and the Dutch reference product are (virtually) identical (§1.3.7)
21. Information to underpin a change in the contents of the packaging for the parallel product (§1.3.8)
22. Sample of the parallel product (§1.3.9)
23. Braille declaration (§1.3.19)
24. Declaration regarding batch release of blood products and vaccines (§1.3.20)

25. Colour mock-up of the new outer packaging (secondary packaging) and separate document with packaging text
26. A declaration that the proposed packaging size is not available on the market in the country of origin and that the proposed packaging size has been approved for the Dutch reference product

The sections below provide a further explanation of the requirements for a parallel application dossier.

B. Structure of submission

The MEB has established an electronic format for parallel applications. It has been obligatory to use this after 12 August 2015. Parallel applications submitted after this date that do not conform to the electronic format for parallel authorisations will not be processed. More information about this format is available on the MEB website.

1.3.2 Application letter

The application letter must at least contain the following information:

- That this is a request for awarding of a marketing authorisation for a product for parallel importation
- Proposed product name
- Country of origin
- RVG number of the Dutch reference product
- The legal entity/person submitting the application (the future parallel marketing authorisation holder)
- The name and full address of the manufacturer(s) responsible for the re-packaging and release of the parallel product that is the subject of the application
- The name, the telephone number and the e-mail address of the person who is conducting the application on behalf of the legal entity/person (contact person). This person must sign and date the application letter.

1.3.3 Application for a parallel import marketing authorisation

The template for the application for awarding of a parallel marketing authorisation is available on the MEB website.

The application for awarding of a parallel marketing authorisation must at least contain the following details:

1. The proposed product name.
2. The legal entity/person submitting the application (the future parallel marketing authorisation holder).
3. The name of the person who is conducting the application on behalf of the legal entity/person. This person must sign and date the application.

1.3.4 Comparison form

The template for the comparison form is available on the MEB website.

The comparison form clearly states which data must be completed. The following points are important:

1. The comparison form must be signed and dated by the Qualified Person who will release the parallel importation product once it has been labelled in Dutch or following complete repackaging and replacement of the foreign package leaflet by a Dutch package leaflet.
2. The entire comparison form does not have to be completed if the parallel product and the Dutch reference product have completed the same MRP/DCP. The reason for this is that - in this case - the parallel product and the Dutch reference product are exactly the same product (the same authorisation dossier). The comparison form clearly describes which minimum information must be provided in this situation.

Under 2: A copy of the MRI product index must be added to the application dossier in the event that a parallel importer claims that the parallel product and the Dutch reference product have completed the same MRP or DCP. This can be added as an appendix to the comparison form.

1.3.5 Comparison photograph and photograph of parallel product

The application dossier must include a comparison photograph, depicting both the Dutch reference product and the parallel product, as well as (all sides, including the inner side if it contains information, of) the inner and outer packaging and - if relevant - the further contents (e.g. applicators, measuring jugs and injection needles) of both products. For included medical devices the CE marking, manufacturer and dimensions must be visible. Based on this information, the MEB will assess whether the products differ in appearance, method of preparation and/or administration and/or (contents of) the packaging in such a way that it could result in the parallel product and reference product not being considered identical or virtually identical.
However, it is possible that the Dutch reference product is not available on the market, meaning that the parallel applicant is unable to submit the required comparison photograph. The parallel importer should state this clearly in the application dossier. The MEB will then consult other sources to assess whether both products are (virtually) identical.

A colour photograph of the parallel product should always be submitted, with all sides of the inner and outer packaging and the entire contents clearly visible. Also refer to §1.3.14.

1.3.6 Foreign SmPC

In the event that the parallel importation product needs to be dissolved or diluted before use, the comparison form must state which solvents or dilutants the parallel and reference

products are compatible with. This also applies to the final concentration (range) after dilution, if relevant.

This information must be obtained from the SmPC for the product. This means that the foreign SmPC must be consulted for the parallel product. This foreign SmPC, as well as an authorised translation of the relevant section, must form part of the application dossier. The foreign SmPC does not have to be included only if a **complete** description of the compatibility with certain solvents or dilutants and the final concentration (range) are included in the foreign package leaflet. After all, the foreign package leaflet always has to be included in the application dossier. It remains essential to submit an authorised translation of the relevant section(s) of the foreign package leaflet (see §1.3.13).

The requirement to submit information relating to compatibility with certain solvents or dilutants and the final concentration (range) does not apply if the parallel and reference products form part of the same MRP or DCP.

If the foreign SmPC was used as a source for other information in the comparison form, it must also be added to the application dossier, including an authorised translation of the sections that are referred to.

1.3.7 Additional information about being identical/virtually identical

If there are one or more differences between the parallel product and the reference product (particularly differences in the characteristics listed under §1.2.1), one must underpin why both products can nevertheless be considered identical/virtually identical.

1.3.8 Change in packaging contents

If the parallel importer wishes to change the contents of the packaging for parallel importation in order to ensure that the parallel product is identical or virtually identical to the reference product, this change and the reason underpinning it must be included in the application dossier. If the parallel applicant wishes to add or replace a device, (quality) data for the device (e.g. details of manufacturer and CE marking and proof of dosage accuracy) must also be submitted so that the MEB can assess whether the device is comparable in use and quality to the approved device for the reference product. Also refer to §1.2.2.

The adaptation of the packaging size is subject to the conditions described in §1.3.15-B).

1.3.9 Sample of the parallel import product

There is no standard requirement to submit samples of the product for parallel importation. However, the parallel importer must have a sample available and submit this sample if requested to do so by the MEB.

1.3.10 Nomenclature of parallel product

The MEB strongly prefers that the parallel importer selects the name used for the Dutch reference product. This reduces the risk of confusing the user.

If the Dutch reference product has a name that is no longer permitted according to the current nomenclature policy ("Nomenclature of pharmaceutical products", MEB 13), the MEB will accept the use of a name in the "old style" for the parallel product.

If the applicant suggests a product name that is not identical to that of the reference product, this will only be accepted if the name meets the requirements of the current MEB nomenclature policy.

1.3.11 Proposed package leaflet

A. Verbatim/concurrent

The package leaflet for the parallel product must be **verbatim the same** as the Dutch reference product as far as the sections on indications, contra-indications, adverse events, dosage, method of use and method of administration are concerned. The other sections of the package leaflet must be concurrent, preferably verbatim, to the reference package leaflet, with the exception of those sections of the package leaflet that contain parallel-specific information, see section §1.3.11-B. A declaration to this effect must accompany all applications. The template for this package leaflet declaration is available on the MEB website.

In general, all the requirements for the package leaflet of the Dutch reference product also apply, as described in the policy document "Package leaflet of pharmaceutical products" (MEB 5). Annex 1 'Explanation of package leaflet sections in the QRD template' in MEB 5 contains an upside down triangle (▼) as a symbol for products 'subject to additional monitoring'. This symbol is used on the SmPC, package leaflet and on any educational materials. If this symbol is present on the package leaflet (and any educational materials) of the reference product, the package leaflet (and any educational materials) the parallel product must be added accordingly, see also under §1.3.16.

If the reference medicinal product is a medicinal product that has been authorised without Dutch translations, the MEB will ask the marketing authorisation holder of the reference medicinal product with English product information to submit a high quality Dutch translation of the product information within 1 month. Please also refer to the Policy Document MEB 41 'Policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups'. The parallel package leaflet should be based on this Dutch version of the package leaflet (see also § 1.6).

B. Stating parallel-specific information

Attention must be paid to the correct reporting of the parallel-specific information in the proposed package leaflet, i.e. the characteristics for which the parallel product may differ from the reference product, namely:

1. **Product name**
   This must be stated completely and clearly recognisably at the top of the package leaflet, even in the case of a combined package leaflet.
   If the product name in the country of origin differs from that of the parallel product, section 6 of the package leaflet must state the product name in the country of origin by means of the following standard sentence: '*The product mentioned in this package leaflet is marketed in the country of origin under the name <foreign product name>*".
   NB. Given that a parallel marketing authorisation concerns a national authorisation, it is not permitted to include the text "*This medicinal product is authorised in member states of the EEA under the following names: "The Netherlands + country of origin*" in the package leaflet.
2. **Excipients**
   The excipients of the parallel product must be stated in the package leaflet as they are in the foreign package leaflet.
3. **Warning for excipients**
   Warnings for certain excipients as stipulated in the "Guideline on the excipients" (MEB 08) must be included, if applicable. (Please note that the relevant excipient must also be listed on the label, followed by a reference to the package leaflet, such as: '*Please read the package leaflet for further information*').
4. **Method of preparation and/or administration**
   The method of preparation and/or administration (this includes the compatibility with certain solvents/dilutants and the final concentration (range), if relevant for the product) must be included where applicable to the parallel importation product.
5. **Instructions for correct use on the primary packaging**
   If the foreign primary packaging contains instructions for correct use, these instructions must be placed in Dutch on the parallel labelling (also refer to §1.3.15-B). However, if re-labelling of the primary packaging is not possible (refer to §1.3.15-A), a translation of these instructions must be included in the parallel package leaflet. This applies, for example, to calendar packaging where the abbreviations of the days of the week are stated in a language other than Dutch on the foreign strip or blister packaging. These abbreviations must then be translated in the package leaflet.

   Please note: if the contents of the packaging (e.g. addition/removal of device) are amended because this is essential to ensure that the parallel product is (virtually) identical to the Dutch reference product, the foreign instructions for use may no longer apply (completely). The instructions for use then need to be amended. If changes to the contents of the packaging ensure that the use and administration are exactly identical to the reference product, the text included in the reference package leaflet may be copied verbatim.

6. **Contents of the packaging**
   The contents of the packaging must be stated exactly as the parallel importer wishes to market it in the Netherlands.
7. **Package size**
   The package size listed in the package leaflet must correspond to the package size that will actually be imported. If the packaging size is changed, the new packaging size must be stated (see also § 1.3.15-B).
8. **Storage conditions (before and after opening and further preparation) and storage period after being brought into use**
   The storage conditions of the parallel importation product (before and after opening, after further preparation) and - if relevant - the shelf life after being brought into use, as approved in the country of origin must be stated in the proposed package leaflet. (See §1.2.1-E).
9. **Dosage schedule (more pharmaceutical forms and strengths)**
   If the package leaflet of the Dutch reference product contains more strengths than the package leaflet of the parallel product, this can have consequences for the feasibility of the dosage instructions and even the indication(s):
   a. If not all the dosages are feasible with the requested parallel product, this must be stated using the following standard sentence in the parallel package leaflet: *'The recommended dosages cannot all be achieved with <this product> <these products>, however, other products with a lower strength than <strength> are also available'*.
   b. If it turns out that the patient needs to use a very large number of tablets, capsules, etc. to achieve the recommended dosages, the following sentence can be included: '*The recommended dosages can be achieved with this product. However, other products with a higher strength than <strength> are available, which means fewer tablets need to be taken per dosage.'*
   c. If certain indications are not feasible with the requested parallel product, this indication and any information related to this indication must be removed from the parallel package leaflet.
10. **Description of appearance of parallel product**
    If the package leaflet of the Dutch reference product states the appearance (such as the shape, colour and presence and function of the break line) of the product, such information must also be included in the package leaflet of the parallel product. Of course this information must refer to the details of the product for parallel importation.
11. **RVG number**
    The complete RVG number of the parallel product must be stated on the package leaflet (and on the label). At the time of submission of the application, the parallel importer only knows the RVG2 (the RVG number of the reference product). Therefore, the MEB will complete the RVG1 on the package leaflet and on the label. The parallel applicant must do the same for the printed versions of the package leaflet and the label.
12. **Country of origin**
    The country of origin must be stated, preferably after the RVG number (e.g. as follows: 'C.o.o.: Greece').

13. **Release manufacturer**
    The release manufacturer(s) of the product for importation must be stated in the package leaflet. Even if there are no manufacturers listed in the Dutch reference package leaflet, the release manufacturers of the product for importation must still be added to the parallel package leaflet.
14. **The date of approval and version management**
    The date of approval will be completed by the MEB. This is the date on which the package leaflet is confirmed by the MEB. The QRD text *'This package leaflet was last approved in [Month Year]'* must be used in this regard.

Due to a possible infringement of trademark law, the parallel applicant is also allowed to include the following information in the package leaflet and/or the label/the new outer packaging:

15. **Origin of included accessory**
    If the parallel applicant has added an item to the packaging, the origin of this item can be stated in the package leaflet and/or on the label/the new outer packaging.
16. **Name of original authorisation holder**
    The name of the original authorisation holder in the country of origin can also be included in the package leaflet and/or on the label/the new outer packaging. However, this must occur in such a manner that it does not result in confusion for the user about who is responsible for marketing the parallel product on the Dutch market.
    (See §1.3.15-B and -C).

Combined package leaflet

A "combined package leaflet" refers to both the combining of various strengths or pharmaceutical forms of a certain product in one package leaflet and to the inclusion in one package leaflet of several products with the same strengths and pharmaceutical form that have been imported from various countries. In general, both situations are permitted for parallel package leaflets. The various products in the combined package leaflet can differ in product name, strength, package size, storage conditions etc. The combined package leaflet must state clearly which data apply to which product. This must be achieved by at least stating the RVG number after the (product-specific) information that applies to that product. More distinguishing characteristics are permitted.

However, if there are many differences between the parallel-specific information of the various products in the combined package leaflet, this can result in the package leaflet becoming unclear or confusing. In that case separate package leaflets must be drafted for the various products.

1.3.12 Information for the medical professionals

As stated in the document "Package leaflet for pharmaceutical products" (MEB 5), in the case of parenterals and other pharmaceutical products that are usually used in hospitals, information for medical professionals must be added in addition to a package leaflet containing information for the patient. The information intended for the patient and for the medical professionals must be clearly separated. This can be achieved in the form of two

separate package leaflets (patient package leaflet and information for the medical professionals), or through the inclusion of information for the medical professionals under a perforation line at the end of the package leaflet.

If the reference product contains information for the medical professionals, this information must also be included for the parallel product. The information for the medical professionals must be identical (verbatim) to the information for the reference product, except for the parallel-specific information (as stated under §1.3.11-B). The information for the medical professionals, as well as a signed declaration that this information is verbatim for the parallel and reference products, should be added to the application dossier. The template for the declaration is available on the MEB website. In addition, the following sentence should be included below the patient package leaflet:
<The following information is intended only for doctors or other healthcare professionals>.

If the information for medical professionals for the reference product consists of the entire SmPC, the product-specific information for the parallel product must be adopted correctly when copying this SmPC for the parallel product (refer above under §1.3.11-B). The information in section 6.3 of the SmPC of the reference product, the shelf life, must **not** be copied. Instead, a reference must be made to the shelf life as stated on the label, as is the case for section 5 of the package leaflet for the patient. The reason is that the shelf life as approved by the foreign authority for the product for parallel importation can differ from the shelf life of the Dutch reference product, if both products have not completed the same MRP/DCP.

Please also refer to the policy document “Package leaflet for pharmaceutical products” (MEB 5).

1.3.13 Authorised translation of the foreign package leaflet and - if relevant - the SmPC

The applicant must submit a Dutch or English authorised translation of the package leaflet valid in the country of origin for the parallel importation product, if (1) the package leaflet is drafted in a language other than Dutch, English, French or German and (2) if the Dutch reference product and the parallel importation product have not completed the same MRP/DCP.

At the time of the application, a translation only needs to be submitted for the passages that contain the following information:

1. Qualitative and quantitative composition of the active ingredient(s) and the qualitative composition of the excipients
2. Pharmaceutical form
3. Storage temperature and conditions, also (if relevant) after opening or reconstitution
4. Processing instructions (method or reconstitution, the solvents used and whether these are included or not / the use of listed devices, such as nebulisers and spacers and whether these devices are included or not)

5. The legal persons listed in the package leaflet and their capacity (authorisation holder, manufacturer, licence provider if applicable, licensee etc.)
6. If relevant: information pertaining to the compatibility with certain solvents/dilutants and final concentration (range) (see §1.3.6).

The rest of the package leaflet does not need to be translated at the time of the application. A complete translation is only required in the event of withdrawal of the reference product, if the parallel authorisation holder wishes to continue with the parallel marketing authorisation (see section 3).

If the information listed under point 6 is not (fully) included in the foreign package leaflet, this information must be obtained from the foreign SmPC. An authorised translation of the relevant section(s) of the foreign SmPC must then be submitted, unless the SmPC is drafted in Dutch, English, French or German. This also applies if the SmPC is used as a source for other information in the comparison form. (See §1.3.6).

1.3.14 Foreign packaging

Information on the foreign packaging that contradicts (1) the Dutch SmPC and/or (2) the Dutch labelling policy 'Labelling of pharmaceutical products' (MEB 6) must be rendered illegible and a declaration about this redaction and the method of redaction (e.g. taping or covering with marker) must form part of the application. Whether or not the redaction method is acceptable, will be assess by the MEB on a case-by-case basis.

The foreign package leaflet should be replaced by the Dutch package leaflet, see also §1.3.11.

It is not permitted to open the primary packaging because this will have detrimental consequences for the quality, safety and/or efficacy of the product.

Under 1: In the case of **OTC medicinal products** the indications, contra-indications and dosages stated on the packaging must be rendered illegible if they differ from those approved for the Dutch reference product.

The following applies to both prescription and OTC medicinal products: information about a **route of administration** that is no longer/not approved in the Netherlands must be rendered illegible.

Furthermore **QR codes** on the foreign packaging must be rendered illegible. QR codes refer to a foreign website, which does not fall under the responsibility of the parallel authorisation holder and the contents of this website could cause confusion if it does not match the SmPC of the Dutch reference product. The parallel authorisation holder is allowed to place his own QR code on the label. The rules as drafted in the MEB's QR policy apply, as stated on the MEB website.

Under 2: Logos, signs and/or pictograms on the foreign packaging that contradict the policy document MEB 6 and that have previously been rejected for the Dutch reference product must be rendered illegible.

Exception:
The text "*Teil einer Klinikpackung - Einzelverkauf unzulässig*" does not need to be rendered illegible, in accordance with a previous ruling by the MEB.

1.3.15 Proposed labelling text and new outer packaging

A. Obligation to provide new labelling/outer packaging again

According to the Medicines Act, the inner and outer packaging of a medicinal product that is marketed in the Netherlands must be in Dutch. This also applies to parallel products. The parallel importer must therefore either label **both** packages again, or re-label the primary packaging and then place the product in a new outer packaging (see also D and E).
It is important to note that the re-labelling/re-packaging should not result in a change or deterioration in the condition of the medicinal product (Article 7 of Directive 2008/95/EC, the first brand directive, previously 89/104/EEC). The MEB will not adhere to the requirement of re-labelling the primary packaging, if this is detrimental to the patient. Examples of this include being able to remove tablets from a blister. If the parallel applicant is of the opinion that the re-labelling of the primary packaging will change/worsen the condition of the product, the underpinning for this must be submitted as part of the application dossier. Furthermore, if the parallel applicant wishes to re-package the product entirely, the MEB will assess whether this is detrimental to the original condition of the product.

B. Requirements and conditions for the Dutch label/the new outer packaging

The Court of Justice of the European Union has set five conditions in the joined cases C-427/93, C-429/93 and C-436/93, which apply to both the newly packaged and newly labelled product. These conditions relate to:

I. New packaging is essential to allow marketing of the product in the country of importation;
II. The new packaging does not harm the original state of the product in the packaging;
III. The new packaging clearly states who is responsible for the packaging and also states the original authorisation holder in the country of origin. This also applies to the origin of items added to the packaging by the importer. (Also refer to C and D);
IV. The presentation of the re-packaged product may not result in damage to the reputation of the brand and the brand rights holder (for example, the packaging may not be defective, of poor quality or look scruffy); and
V. The parallel importer will inform the brand rights holder about the re-packaging before marketing the product. In addition, if requested, the importer will give the brand rights holder a sample of the re-packaged product.

If one or more of the above-mentioned conditions is/are not met, the brand rights holder can object to the re-labelling/re-packaging.
The MEB is not involved in matters regarding the brand rights, but merely checks the first three conditions during a parallel application for other reasons as stated in this policy document, based on the following conditions:

1. Is re-packaging (including changes to the contents of the package, see §1.3.8) necessary in order to make the parallel product (virtually) identical to the reference product and/or is re-packaging necessary due to the Falsified Medicines Directive (FMD)? (Directive 2011/62/EU, see for more information the Q&A of the European Commission on the implementation of the delegated regulation 2016/161 (https://ec.europa.eu/health/human-use/falsified_medicines_en#).
2. Is re-labelling/re-packaging in no way detrimental to the user? (Also refer to A)
3. Is the party responsible for re-labelling/re-packaging stated on the label/the new outer packaging? (Also refer to C and D).

In addition, the MEB has the following requirements regarding the new label or the new outer packaging:

4. Information specific to the parallel product must be stated correctly, see further under C.
5. Important warnings or restrictions on the packaging of the Dutch reference product must be copied, see further.
6. Instructions for correct use on the foreign (primary) packaging (e.g. the days of the week or abbreviations thereof in the case of calendar packaging) must be copied correctly in Dutch on the label.
7. If re-labelling of the primary packaging is not possible (refer to A), a translation of these instructions must be included in the package leaflet (also refer to §1.3.11-B).
8. The labelling text/outer packaging must meet the requirements of the policy document “Package leaflet for pharmaceutical products” (MEB 6). This also means that, in the event of a new outer packaging, the packaging of the various pharmaceutical forms and strengths from the same parallel marketing authorisation holder can be clearly distinguished from each other.
9. The labelling text/outer packaging must meet the requirements of the “Guideline on readability” (particularly font size). This entails that the font size of the packaging text must be at least 7 points Didot. (For more information, please refer to the policy document “Labelling of pharmaceutical products” (MEB 6)).
10. The information must be stated clearly on the label/packaging.

In addition, the following applies to **OTC medicinal products**:

11. **(Contra-)indications:**
    The indication(s) and contra-indication(s) must be stated on the label; the information must be identical (verbatim) to the indication(s)/contra-indication(s) as stated on the packaging of the Dutch reference product.
12. **Dosage, method of use and method of administration:**
    If the packaging of the Dutch reference product states the dosage, the method of use and/or the method of administration, this information must be copied verbatim on the labelling text of the parallel importation product.

If the **packaging size** is adapted, the following two conditions still apply:

13. The packaging size may only be adapted if the desired packaging size is not available on the market in the country of origin.

14. Changing the packaging size makes it identical/virtually identical to a packaging site registered for the Dutch reference product (as stated in the SmPC/package leaflet). It is not permitted to change the packaging size of the product to be imported into a packaging size which differs substantially from the packaging size(s) registered for the Dutch reference product. See also §1.2.1-A+F.

Under 6: Important warnings or restrictions on the packaging of the Dutch reference product (e.g. "to be used by men only") must also be copied on the label of the parallel product. It has been decided for the reference product that this warning is essential to ensure correct use of the product. The information that is included must be similar to the information on the packaging of the reference product. (Please also refer to the policy document "Labelling of pharmaceutical products" (MEB 6)).

Under 13 and 14: The parallel applicant should include a declaration in the application letter to the effect that the proposed packaging size is not available on the market in the country of origin and that the proposed packaging size has been approved for the Dutch reference product.

Under 13: If separate foreign packages in a multipack display a statement on separate sales (e.g. "Part of a multipack – not to be sold separately") and the multipack is split up, the statement must be rendered illegible (for example by taping or covering with marker – see also §1.3.14) in order to avoid confusing the user and/or professionals. However, splitting up the multipack and taping over the statement will remain the responsibility of the parallel applicant. To prevent any conflicts, the MEB recommends informing the brand rights holder about the proposed course of action. See also §1.3.15.B.

The parallel applicant is also allowed to place his own QR code on the packaging (see §1.3.14).

C. Stating parallel-specific information

The information that must be included on the labelling text/outer packaging of the parallel product is described in the policy document "Labelling of pharmaceutical products" (MEB 6). In addition, attention must be paid to the correct listing of the parallel-specific information, namely:

1. **Product name**
   The product name must be the same as the product name stated on the application document and in the proposed package leaflet.
2. **Excipients**
   If the product contains an excipient listed in the "Guideline on the excipients in the label and the package leaflet of medicinal products for human use" (MEB 8), this excipient must be listed on the label followed by "*Read the package leaflet for further information*". This also applies if the packaging of the reference product does not contain such information.

In the case of products for **parenteral administration**, for **local use** and for **the eye**, the (primary and secondary) label must also state all excipients. If the composition of the parallel product differs from that of the reference product, it is important to ensure that the composition of the parallel product is stated.

3. **Storage conditions (before and after opening and further preparation) and storage period after being brought into use**
   The storage conditions of the parallel importation product (before and after opening, after further preparation) and - if relevant - the shelf life after being brought into use, as approved in the country of origin must be stated. (See §1.2.1-E).
4. **Package size**
   The stated package size must correspond to the size stated in the comparison document and on the (comparison) photograph. If the packaging size is changed, the new packaging size must be stated (see also § 1.3.15-B).
5. **Re-packager and release manufacturer**
   *Please refer to D below for information on the separate requirements for stating the re-packager and the release manufacturer.
6. **Country of origin:**
   It is preferable, but not mandatory, to state the country of origin (or the abbreviation).

Due to a possible infringement of trademark law, the parallel applicant is also allowed to include the following information in the package leaflet and/or the label/the new outer packaging:

7. **Origin of included accessory:**
   If the parallel applicant has added an item to the packaging, the origin of this item can be stated in the package leaflet and/or on the label/the new outer packaging.
8. **Name of original authorisation holder:**
   The name of the original authorisation holder in the country of origin can also be included in the package leaflet and/or on the label/the new outer packaging. However, this must be done in such a manner that it does not result in confusion for the user regarding who is responsible for marketing the parallel product on the Dutch market, for example by using the text 'Authorisation holder in the country of origin: [name of authorisation holder]'.
9. **Clearance manufacturer:**
   The name of the clearance manufacturer in the country of origin must be included in the package leaflet and can also be included on the label/the new outer packaging. However, this must be done in such a manner that it does not result in confusion for the user regarding who is responsible for releasing the batches of the parallel product in the Netherlands. The information must therefore be stated as follows: 'Manufacturer in the country of origin: [manufacturer's name]'. The manufacturer must be considered to be the clearance manufacturer that is referred to in the foreign package leaflet of the imported packaging'. If several clearance manufacturers are referred to in the package leaflet, these must all be referred to, or the parallel applicant can choose one of the manufacturers.

D. Party responsible for re-packaging and the release manufacturer

Stating re-packager

The re-packager is the company that re-labels the parallel product or gives it an entirely new outer packaging.

Stating the legal person (name and address) responsible for the re-packaging (name and address) on the packaging of the parallel product is a brand right requirement, in accordance with Article 7 of Directive 2008/95/EC and is therefore **mandatory**. This means that both the actual re-packager and the authorisation holder who gives instructions for the re-packaging and who accepts responsibility for the re-packaging may be stated as re-packager on the label. (This in accordance with the ruling by the Court of Justice of the European Union, dated 28 July 2011, regarding cases C-400/09 and C-207/10).

Article 7 of Directive 2008/95/EC must be interpreted such that the original authorisation holder can appeal against marketing of his product by a parallel importer if the re-packager is not mentioned. After all, the re-packaging/re-labelling is not performed at the request or under the responsibility of the original authorisation holder and any change or deterioration in the condition of the product is therefore not the responsibility of the original authorisation holder.

In case the re-packager and parallel marketing authorisation holder are the same, or if the latter is taking responsibility for re-packaging, the standard text on the label is 'authorisation holder/re-packager:'.

Stating release manufacturer

In the case of radiopharmaceuticals, stating the release manufacturer on the label is mandatory (see “Labelling of pharmaceutical products” (MEB 6)). This obligation does not apply to all other products.

E. Complete re-packaging

Instead of re-labelling the secondary packaging, the parallel importer can also completely re-package the product. The following requirements apply with regard to the parallel application dossier:

- The application must not only include a flat label text, but also a full-colour mock-up of the new outer packaging (secondary packaging).
- The printed text on the new outer packaging must meet the same requirements as a Dutch label, see under A and B.
- The new outer packaging must include Braille text and the accompanying Braille declaration must be submitted, see under §1.3.19.

Please refer to B for the other conditions relating to re-packaging.
If the product is going to be re-packaged, the primary packaging must still be given a new label, see under A.

1.3.16 Additional risk minimisation measures (aRMM)

For some products, there are additional requirements regarding information for the user and/or healthcare practitioner, known as the educational material. An example of this is the patient card. This card contains important instructions for use of the product. If this educational material is available for the Dutch reference product, this must also be submitted for the parallel product.

This educational material must be drafted in Dutch. The educational material must be verbatim identical to that of the Dutch reference product, including the upside-down triangle (▼) as a symbol for products 'subject to additional monitoring' (see under §1.3.11-A). The parallel applicant must include a declaration to this effect in the application letter.

The name of the Dutch reference product must be replaced with the name of the active ingredient. In addition, the name of the marketing authorisation holder for the Dutch reference product must be replaced with the name of the parallel marketing authorisation holder.

The following sentence must be included in the material: 'The name and contact details of the authorisation holder are stated on the packaging and in the package leaflet.' This refers to the name and contact details of the parallel applicant.

The Medicines Information Bank on the MEB website can be consulted to check whether educational material has been confirmed for a certain product. The parallel applicant must check this before submitting an application for awarding of a parallel marketing authorisation. The proposed educational material must form part of the application dossier.

It may happen that educational material for a reference product has been adopted at the European level, even though the reference product itself is not available on the market. In that case, the educational material will not be present in the Medicines Information Bank and will still need to be translated and implemented. A distribution plan must also be submitted in that case.

The MEB will determine during the assessment of these parallel applications and the educational material whether active distribution is required and - if so - to which target groups.

Also refer to the policy document for marketing authorisation holders: National implementation of additional risk minimisation measures (MEB 45).

1.3.17 Authorisations

A copy of the required authorisation(s) or a reference to EudraGMP must be included in the parallel dossier.

The following authorisations are relevant for parallel marketing:

A. Manufacturing authorisation (supplemented if necessary by a GMP certificate):
- A valid manufacturing authorisation is essential for permission to re-package/re-label, release and/or supply parallel imported products. A valid manufacturing authorisation must be submitted for all legal persons involved in one or more of the listed actions.
- If the manufacturing authorisation is older than three years, it must be supplemented by a valid GMP certificate that is not older than three years.

B. Wholesale authorisation:
- Usually a manufacturing authorisation will suffice for parallel marketing. Although the importer is obtaining medicinal products from within the EEA, these are “self-prepared medicinal products” due to re-packaging/re-labelling. A wholesale authorisation is only required for legal persons who are re-selling or supplying the purchased medicinal products, without performing any preparation steps or without release. In that case the legal person is selling/supplying medicinal products from third parties.
- A wholesale authorisation issued by another EU country is only valid in the Netherlands if the wholesale activities take place exclusively in other countries. If wholesale activities (also) take place in the Netherlands, a Dutch wholesale authorisation is (also) required.
- The wholesale authorisation is granted for an indefinite period.

C. Parallel wholesale authorisation:
- Before the Medicines Act was enforced (1 July 2007), there was the parallel wholesale authorisation. These authorisations were awarded for an indefinite period and are still legally valid, but are no longer awarded. In terms of the Medicines Act, a parallel wholesale authorisation is equal to a limited manufacturing authorisation in combination with a wholesale authorisation.

An authorisation is not required for merely purchasing medicinal products.

Please contact the CIBG for more information regarding the authorisations required for parallel importation.

1.3.18 Addendum expansion of European Union ('specific mechanism')

New rules for parallel importation came into effect with the admission of ten new member states to the European Union on 1 May 2004. These rules were updated in 2007, following admission of Romania and Bulgaria. The rules relate to agreements between the EU and the new member states in order to prevent the importation of products from a new member state to an “old” member state where a patent or additional protection certificate applies

for that product. This relates to the so-called “specific mechanism” included in the admission treaties.

The reason for this is that the new member states offered more limited protection than the “old” member states prior to the admission to the EU of the new member states. If a medicinal product from Bulgaria, Estonia, Hungary, Croatia, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia or the Czech Republic is imported to an “old” member state where a patent or additional protection certificate still applies to that product, the holder of the patent or the additional protection certificate, or his beneficiary, can object to the parallel importation due to infringement of patent rights. Therefore, the legal person - who wishes to import a medicinal product via the parallel route from a new member state to an “old” member state where a patent or additional protection certificate applies for that product - must inform the patent holder about this intention one month prior to submitting an application to the MEB. This will inform the patent holder of this intention and provides adequate time to submit a legal objection to the parallel importation.

The parallel importer must demonstrate with the parallel application that the holder of the patent or the additional protection certificate, or his beneficiary, was notified about the proposed parallel importation at least one month prior to the parallel authorisation being awarded. To this effect, a completed and signed “Declaration Member State of origin parallel importation” and a copy of the notification to the holder of the patent or the additional protection certificate must be added to the application dossier. The template for the declaration is available on the MEB website.

If there is no patent or additional protection certificate on the parallel product, the parallel importer must submit a declaration to this effect - instead of the above-mentioned documents - as part of the application dossier.

The above-mentioned is also described in Art. 48, section 7, of the Medicines Act.

1.3.19 Braille

European legislation (Art. 65a of Directive 2001/83/EC) stipulates that the product name must also be stated in Braille on the packaging. However, the Braille requirements for parallel importation differ from those for non-parallel products:

1. **There is no Braille present on the foreign packaging:**
   - The parallel applicant is not required to place Braille on the packaging.
   - If the parallel importer decides that he wants to use Braille, the same requirements apply as for a non-parallel product.
2. **There is Braille present on the foreign packaging:**
   If the product name in the country of origin differs from the name in the Netherlands, the product name in the country of origin can be retained in Braille. The Dutch product name does not need to be added in Braille. However, the Braille must remain legible after re-labelling. The Braille may be written through the printed text.
3. **The parallel importer will re-package the product:**
   In that case, the parallel importer must place Braille on the new packaging.

The parallel applicant only needs to submit a Braille declaration if the applicant is responsible for adding Braille to the packaging. This declaration is not required if the Braille already formed part of the foreign packaging before importation.

1.3.20 Declaration regarding the release of blood products and vaccines in batches

If the product for parallel importation concerns a blood product or vaccine, one of the following declarations must be submitted:

- A declaration that the product was imported from a country where additional release in accordance with Article 114 of Directive 2001/81/EC, as amended via Directive 2004/27/EC, is mandatory;

or, if this declaration cannot be made,

- Information about how the applicant will ensure that the batches have been released by a government authority appointed for this task. (An acceptable answer would be that the applicant declares that they have reached an agreement with the National Institute for Public Health and the Environment (RIVM) that the latter will check whether the batches have undergone additional release for the European market).

The parallel applicant can include this declaration in the application letter. There is no template available on the MEB website.

For more information, please refer to section 1.5.

1.4 Common origin

A requirement for parallel applications in the past was that the parallel product and the Dutch reference product were produced by the same manufacturer or by manufacturers belonging to the same concern (common origin). The reason for this was that this resulted only in importation of a product to the country of importation that was equal to a product already approved in that country (the reference product). Due to a ruling by the European Court in the so-called Kohlpharma decree (case C-112/02, dated 1 April 2004) this requirement of common origin no longer applies however. The ruling by the Court meant that - from that point on - a foreign, generic product could also be imported to another country, provided that the innovator for which therapeutic equivalence (interchangeability) was demonstrated also had a marketing authorisation in the country of importation.
In the case of a parallel application without common origin, the MEB will assess whether the product is therapeutically equivalent to the Dutch reference product (i.e. that the products are identical, or virtually identical). The application can only be accepted if therapeutic equivalence is confirmed. This is in line with Art. 48, section 1, of the Medicines Act.
(Also refer to §1.2.1).

1.5 Parallel importation of blood products and vaccines

Batches of blood products and vaccines, including parallel importation products, must be released by an appointed government authority, the Official Medicines Control Laboratories (OMCL), before being marketed. The OMCL in the Netherlands is the National Institute for

Public Health and the Environment (RIVM). The OMCL determines whether the batch meets the approved specifications before being released to the market. A certificate is awarded in the case of a positive result.

The requirements regarding batch release (Official Control Authority Batch Release (OCABR)) of vaccines and blood products are included in Article 114 of Directive 2001/81/EC, as amended via Directive 2004/27/EC and incorporated in the Dutch legislation. The foundation for the OCABR is set out in Article 28, Section 6, of the Medicines Act and in Article 6.2 of the Medicines Act Regulations. Article 6.3, Section 1, of the Medicines Act Regulations also stipulates that a blood product or vaccine that has already been released in a member state does not need to undergo further batch release; OMCLs in the EU recognise approval for release from each other. This means that for a batch of a blood product or vaccine that will be imported to the Netherlands, the OCABR procedure does not have to be repeated, provided that additional release by another EU OMCL has already taken place. Giving the RIVM the release certificate awarded by the foreign OMCL will suffice in that case.

However, batch release of blood products or vaccines by an OMCL is not mandatory or fully implemented in a number of EU countries. Therefore, for parallel imported batches of blood products or vaccines from such countries, it cannot be assumed that they have been released by an OMCL. This can be assumed for parallel imported batches of blood products and vaccines originating from the regular channels of EU member states with an obligation to perform additional release.

What does this mean for the parallel application?
One of the declarations listed under §1.3.20 must be included in the application for a parallel marketing authorisation for a vaccine or blood product. If neither of these declarations is included in the parallel dossier, the OCABR will not be guaranteed sufficiently. The parallel marketing authorisation cannot be awarded in this case.

Following the awarding of the parallel marketing authorisation by the MEB, the parallel importer must also report each batch of vaccines or blood products to the RIVM.

The MEB will inform the RIVM of the awarding of a parallel marketing authorisation for a blood product or vaccine by providing a copy of the application letter.

1.6 Use of clock-stop

A parallel application can be placed in clock-stop if:

- the parallel applicant has been asked to provide additional information,
- the MEB needs to obtain information from the authorisation authority in the country of origin in order to rule whether parallel product and Dutch reference product are (virtually) identical,

- the reference medicinal product is a medicinal product that has been authorised without Dutch translations. The MEB must ask the marketing authorisation holder of the reference medicinal product to submit a high quality Dutch translation of the product information within 1 month. The parallel package leaflet should be based on this Dutch version of the package leaflet. (see also § 1.3.11-A).
- an intention of refusal has been sent out, if the MEB concludes that the applicant has failed to demonstrate that the parallel product and the Dutch reference product are (virtually) identical. The policy document entitled 'Written and oral opinion procedure in conjunction with a proposed primary decision by the MEB' (MEB 18) contains more information about the opinion procedure.

In the second case, the MEB will inform the applicant about the clock-stop and the reason for this clock-stop.

The clock will be re-started as soon as additional information has been received from the member state of export or a response has been received from the parallel applicant.

1.7 Tender

The product for parallel importation will be registered by the MEB under the same indications, contra-indications, adverse reactions, dosage, method of use and administration as those for the Dutch reference product. The SmPC that has been approved for the Dutch reference product will also apply to the linked parallel product. The SmPC of the Dutch reference product will be sent out along with the parallel marketing authorisation that has been awarded.

In the event of a combined package leaflet, where one or more products have already been registered, the following request will be included in the notification of registration:
"This is a combined package leaflet with one or more previously registered parallel products. The MEB has replaced the package leaflet of these previously registered parallel products with the version of the package leaflet approved during this procedure. Please update your file accordingly."

The parallel importation product will be registered under RVG1/RVG2, with RVG2 being the registration number of the reference product.

2. Maintenance

2.1 Introduction

The parallel marketing authorisation holder is responsible for keeping the package leaflet up-to-date. Certain variations in the dossier in the country of origin or in the dossier of the Dutch reference product can affect the package leaflet and/or the label for the parallel product. The parallel marketing authorisation holder may also wish to implement variations in the parallel dossier.

All variations, regardless of the origin or the type of variation, should be submitted **a priori** to the MEB for approval. The variation directive does not apply to parallel products.

Variations must be submitted after 12 August 2015 via the prescribed electronic standard structure for parallel products, otherwise the request cannot be accepted for processing (see also §1.3.1- B).

Several variations can be submitted for the same parallel product under one submission (one application letter).

Depending on the type of variation, the following documents must be submitted:

1. Application letter describing the variation
2. Amended comparison form (annotated version)
3. Signed package leaflet declaration
4. Foreign package leaflet
5. Translation of the relevant section of the foreign package leaflet with certificate from a recognised translation agency, if the package leaflet was not drafted in English, German, French or Dutch
6. Amended package leaflet for the parallel product (clean and track changes version)
7. Amended label for the parallel product (clean and track changes version)
8. Amended educational material (clean and track changes version)
9. Photograph of all sides of the foreign packaging
10. New comparison photograph of the parallel product and the Dutch reference product
11. Signed declaration that the new image/the new logo or sign will be rendered illegible on the packaging if it contradicts the Dutch labelling policy
12. A declaration from the current parallel authorisation holder that they agree to the transfer of the parallel marketing authorisation
13. A declaration from the prospective parallel marketing authorisation holder that they will adopt all rights and obligations relating to the authorisation
14. Manufacturing authorisation and/or wholesale authorisation, parallel wholesale authorisation: copy or reference to EudraGMP
15. Additional information about the parallel product and the Dutch reference product remaining identical/virtually identical

16. Colour mock-up of the new outer packaging (secondary packaging) and separate document with packaging text
17. Braille declaration (see under §1.3.19)
18. A declaration that the proposed packaging size is not available on the market in the country of origin and that the proposed packaging size has been approved for the Dutch reference product.

Under 2: It is desirable for the most recent version of the comparison form to be used.

Under 15: In exceptional cases, variations in the parallel dossier can result in the parallel product and the Dutch reference product no longer being (virtually) identical. For each requested variation that is not approved for the Dutch reference product, the underpinning must be submitted that this is not the case.

The following paragraphs describe which documentation must be submitted for a certain type of variation. However, if deemed necessary, the MEB can always ask for more information than stated below.

2.2 Variation in original dossier in the country of origin

This paragraph summarises the variations in the original dossier in the country of origin that affect the parallel dossier.

Variation in package size

- **Origin of variation:** The original authorisation holder in the country of origin has altered the package size via a variation. As a result, the parallel authorisation holder no longer has access to the package size that they previously imported. Therefore, the authorisation holder wishes to import a different package size. See also §1.2.1-A+F.
  If the packaging comes from a different member state to the already registered packaging, it will not be possible to implement this by means of a variation. This will require a new application to be submitted by the parallel marketing authorisation holder.
- **Documentation to be submitted:** 1, 2, 6, 7, 9 (15, if the new package size is not approved for the Dutch reference product)

If the new packaging size is also to be changed, the documentation must be submitted as described under 'Adapting packaging size (content) of the product to be imported' (see §2.4).

Note: The application letter must also include a declaration that no changes will take place in the package leaflet other than the package size.
It is important that the newly imported package size falls within the same legal status of supply and duration of treatment as has been approved for the Dutch reference product. (See also §1.2.1-F).

Variation in release manufacturer

- **Origin of variation:** The authorisation holder in the country of origin has added/removed a release manufacturer to/from the original package leaflet.
- **Documentation to be submitted:** 1, 2, 4, 5, 6, (7, for radiopharmaceuticals and other products in case the release manufacturer is stated on the packaging, see §1.3.15-D)

Note: The application letter must also include a declaration that no changes will take place in the package leaflet (and on the label), other than the information regarding the release manufacturer(s).

Variation in storage conditions and/or shelf life

- **Origin of variation:** The storage conditions and/or shelf life (before/after opening and/or further preparation) has/have changed in the country of origin.
- **Documentation to be submitted:** 1, 2, 4, 5, 6, 7 (15, if the new storage conditions and/or storage period differ from those approved for the Dutch reference product)

Note: The application letter must also include a declaration that no changes will take place in the package leaflet and on the label, other than the information pertaining to the storage conditions and/or shelf life.
(Also refer to §1.2.1-E).

Variation in excipients

- **Origin of variation:** The composition of excipients has changed.
- **Documentation to be submitted:** 1, 2, 4, 5, 6, (7, if relevant, refer to the "Guideline on the excipients" (MEB 08) for the rules for stating excipients on the label), (15, if the new storage composition differs from that approved for the Dutch reference product)

Note: The application letter must also include a declaration that no changes will take place in the package leaflet and - if relevant - on the label, other than the information pertaining to the excipients.
(See also §1.2.1-C).

Variation in external appearance of the product

- **Origin of variation:** The authorisation holder in the country of origin has, for example, decided to change the colour, printing or dimensions of the medicinal product.
- **Documentation to be submitted:** 1, 2, 4, 5, 6, 10 (15, if the new appearance differs from that of the Dutch reference product)

Note: The application letter must also include a declaration that no changes will take place in the package leaflet and on the label, other than the information pertaining to the appearance of the product.

If the variation involves the removal of a break line, then one must check whether the entire dosage instruction and all indications can still be executed. If a break line has been added,

one must check whether the function of the break line is included in the foreign package leaflet; this information must then also be included in the Dutch package leaflet for the parallel product.

Variation in external appearance of the packaging

- **Origin of variation:** The original authorisation holder has, for example, decided to change the dimensions or the image/colours of the packaging.
- **Documentation to be submitted:** 1, 9, 10, (11, if relevant)

Note: It is important to check that no logos or images are added to the new packaging that are not acceptable under the labelling policy. If that is the case, the logo/image must be made invisible and a declaration to this effect must be submitted. (See §1.3.14).

Change in packaging contents

- **Origin of variation:** The contents of the packaging have changed, e.g. as a result of the addition or removal of devices in the packaging.
- **Documentation to be submitted:** 1, 2, 4, 5, 6, 7, 8 (15, if the new contents differ from those approved for the Dutch reference product)

Note: The application letter must also include a declaration that no changes will take place in the package leaflet and on the label, other than the information pertaining to the contents of the packaging.
(See also §1.2.1-D and §1.2.2).

Variation in foreign product name

- **Origin of variation:** The name of the product in the country of origin has changed.
- **Documentation to be submitted:** 1, 2, 4, 6

Note: The application letter must also include a declaration that no changes will take place in the package leaflet, other than the information pertaining to the foreign product name.

2.3 Variation in dossier of Dutch reference product

Variations that are reflected in the SmPC and/or package leaflet of the reference product

- **Origin of variation:** Variations in the dossier of the Dutch reference product will be reflected in the SmPC and the package leaflet. The parallel marketing authorisation holder is responsible for keeping the package leaflet up-to-date and must therefore check the product information of the reference product regularly for relevant variations. The Medicines Information Bank for humans on the MEB website can be consulted for this purpose. The new version of the parallel package leaflet can be implemented after 30 days when no reaction has been received from the MEB. The date at the end of the package leaflet must indicate the month and the year of day 30 of the procedure.
- **Documentation to be submitted:** A request for amendment of the parallel package leaflet must be submitted within three months after amendment of the reference text, including the following documentation: 1, 3, 6, (7, if relevant).

Note: In the event that the amended SmPC is the result, for example, of a variation in the composition of excipients, the administration form or a change in or the addition/removal of a device, this can threaten the interchangeability between the parallel and the reference product, if this same variation is not (yet) incorporated into the original dossier of the product for parallel importation, or if the imported product is an old batch. Such a situation can result in consequences for the parallel marketing authorisation, if the co-existence of two different versions of the product forms a danger to public health. (Also refer to §1.2.1 and §2.1).

Variation in the educational material

- **Origin of variation:** If the educational material for the Dutch reference product changes, a request for amendment of the educational material for the parallel product must be submitted within three months after this variation. The parallel marketing authorisation holder is responsible for keeping the educational material up-to-date and must therefore check the educational material of the reference product regularly for relevant variations. The Medicines Information Bank for humans on the MEB website can be consulted for this purpose.
- **Documentation to be submitted:** A request for amendment of the parallel package leaflet must be submitted within three months after amendment of the reference text, including the following documentation: 1, 8. In the application letter, the parallel applicant must declare that the educational material is identical (verbatim) to that of the Dutch reference product.

Note: The MEB will assess whether the updated material must be distributed actively and - if so - to which target groups. Please also refer to §1.3.16.

2.4 Variation only in the parallel dossier

A parallel marketing authorisation holder can also decide to implement variations in the parallel dossier. The following situations are possible:

Import different packaging size

- **Origin of variation:** The parallel authorisation holder decides to import an additional or different package size. See §1.2.1-A and -F.
- **Documentation to be submitted:** 1, 2, 6, 7, 9 (15, if the new package size is not approved for the Dutch reference product)

NB 1: The application letter must also include a declaration that no changes will take place in the package leaflet other than the package size.
It is important that the newly imported package size falls within the same legal status of supply and duration of treatment as has been approved for the Dutch reference product. (See also §1.2.1-F).

NB 2: The different package sizes must have the same origin. An additional package size, which falls under a different marketing authorisation, or comes from a different member state, must be submitted as a new application and will be fully assessed.

Adapting the packaging size (content) of the product to be imported

- **Origin of variation:** The parallel authorisation holder changes the packaging size of the packaging to be imported. See 1.3.15-B.
- **Documentation to be submitted:** 1, 2, 6, 7, 9 and 18 (15, if the new package size is not approved for the Dutch reference product, 16 and 17 in the event of new outer packaging).

NB 1: It is important that the newly imported package size falls within the same legal status of supply and duration of treatment as has been approved for the Dutch reference product. (See also §1.2.1-F).

NB 2: The different package sizes must have the same origin. An additional package size, which falls under a different marketing authorisation, or comes from a different member state, must be submitted as a new application and will be fully assessed.

Re-packaging in connection with FMD (Falsified Medicines Directive)

- **Origin of variation:** The parallel authorisation holder wants to re-package due to an anti-tampering device on the original foreign packaging.
- **Documentation to be submitted:** 1, 16 and 17.
  If the new packaging size is also to be changed, the documentation must also be submitted as described under 'Adapting packaging size (content) of the product to be imported'.

Note: The printed text on the new outer packaging must meet the same requirements as a Dutch label, see under §1.3.15 B to E.

Variation in parallel authorisation holder

- **Origin of variation:** The parallel authorisation holder transfers the authorisation to another legal person.
- **Documentation to be submitted:** 1, 6, 7, 12, 13, 14

Note: The application letter must also include the following: (a) name, business address, telephone, fax and e-mail address of the current and the new authorisation holder and (b) a declaration that no changes will take place in the package leaflet or on the label, other than the authorisation holder and (if applicable) the product name.
Furthermore, if the variation in authorisation holder results in a variation in product name, both variations can be submitted as one case.

Variation in name and/or address of parallel authorisation holder

- **Origin of variation:** The parallel authorisation holder has changed their name and/or address, but is still the same legal entity.
- **Documentation to be submitted:** 1, 6, 7

Note: The application letter must also include a declaration that no changes will take place in the package leaflet or on the label, other than the name and/or the address of the parallel authorisation holder.

Variation in name of parallel product

- **Origin of variation:** The parallel authorisation holder wishes to change the product name, for example due to commercial reasons, or the name change is the result of a change in authorisation holder.
- **Documentation to be submitted:** 1, 6, 7

Note: The application letter must also include a declaration that no changes will take place in the package leaflet or on the label, other than the product name.
The new product name must meet the regulations described in §1.3.10.
If the variation in product name is the result of a variation in authorisation holder, both variations can be submitted as one case.

Addition of a new legal person in the parallel marketing chain

- **Origin of variation:** The parallel authorisation holder wishes to add a legal person responsible for the re-packaging/re-labelling, release and/or supply of the parallel importation product.
- **Documentation to be submitted:** 7, 14

Note: The application letter must also include a declaration that no changes will take place on the label, other than stating the re-packager.
See §1.3.15-D and §1.3.17.

3. Withdrawal of marketing authorisation for parallel or reference product

3.1 Introduction

This section describes the situation in which the parallel importer decides to request the withdrawal of the parallel marketing authorisation (§3.2) or the situation where the marketing authorisation for the Dutch reference product is withdrawn (§3.3).

3.2 Withdrawal of parallel marketing authorisation at the request of the parallel authorisation holder

A request for withdrawal should be accompanied by a completed and signed application form “Withdrawal of parallel marketing authorisation at the request of the parallel authorisation holder”, which can be found on the MEB website.
In the case of a combined package leaflet, an amended package leaflet (clean and track changes version) and the ‘declaration accompanying a package leaflet of a parallel importation product’ must also be submitted. In the event that the removal of one or more products from the combined package leaflet results in:

(1) all dosages no longer being achievable, this must be stated in the package leaflet by means of the relevant standard sentence, or;
(2) all indications no longer being feasible, then this/these indication(s) and all related information must be deleted from the package leaflet.

(Please refer to the form “withdrawal of parallel marketing authorisation” on the MEB website).

3.3. Withdrawal of marketing authorisation for the Dutch reference product

3.3.1 Introduction

If the marketing authorisation for the Dutch reference product is withdrawn, the linked parallel marketing authorisation(s) continue(s) to exist, unless the MEB sees grounds to withdraw the parallel marketing authorisation(s) due to public health concerns (Art. 48, section 6, of the Medicines Act).

If such grounds exist, the MEB will send out an intention to withdraw the authorisation on the orders of the MEB. The parallel authorisation holder will be asked via this intention of withdrawal to submit underpinning arguments and/or data to demonstrate that keeping the parallel importation product on the market does not pose a risk to public health. If no (convincing) arguments can be submitted, the withdrawal of the marketing authorisation will follow.

3.3.2 Parallel marketing authorisation continues to exist

If the MEB concludes that the parallel marketing authorisation can continue to exist and the parallel importer does not indicate that it wishes to withdraw the parallel marketing authorisation(s), the parallel product will remain linked to the withdrawn reference product. The parallel marketing authorisation holder must then submit a proposal for a new reference SmPC, which will then form a guideline for keeping the parallel package leaflet up-to-date. The SmPC of the withdrawn reference product (RVG2) will be “frozen” from the moment of withdrawal, meaning that the package leaflet for the parallel product can no longer be updated with new insights and therefore will, over time, no longer reflect the current state of affairs. Therefore, a source of information other than the “frozen” SmPC of RVG2 will have to be appointed, which the holder of the parallel marketing authorisation will have to use to keep the package leaflet of the parallel product up-to-date.

There are now two options:
1. The parallel product can be linked to the SmPC of another product authorised in the Netherlands with the same qualitative and quantitative composition of active ingredient(s) and a similar pharmaceutical form (i.e., an improved product, a copy dossier of the reference product, a “second innovator” or a generic).
2. No suitable reference SmPC is found to link the parallel product to. The parallel product will continue without a Dutch reference SmPC.

3.3.3 Link to a new reference SmPC

The parallel authorisation holder must submit a proposal for a new reference SmPC. The MEB will then assess whether this is indeed (the most) suitable.

If the parallel product is linked to a new reference SmPC, the parallel marketing authorisation holder must focus on this new reference SmPC from that point on when updating the package leaflet. Also refer to §2.3.

3.3.4 No link to a new reference SmPC

If the parallel marketing authorisation continues to exist without a reference SmPC, the following obligations apply to the parallel authorisation holder:
1. The parallel authorisation holder must submit a declaration to the MEB, stating that:
    a. the parallel marketing authorisation holder will keep abreast of any variations in the foreign authorisation dossier that could affect the quality, safety or efficacy of the product and will report this to the MEB;
    b. the parallel authorisation holder will follow the recommendations from the PSUSA assessment (which can be found on the EMA website).
2. The parallel marketing authorisation holder must carefully keep track of any variations in the foreign package leaflet (particularly those relating to safety information) and pass this information on to the MEB (see point 3 below). However, this does not mean that entire sections (warnings, interactions, adverse reactions, etc.) of the parallel package leaflet should be amended in line with the foreign package leaflet. Only new safety information must be kept track of and submitted to the MEB.

3. As soon as the parallel importer notices a variation in the foreign package leaflet, the following documentation must be submitted to the MEB:
    a. Application letter, describing the variation
    b. Foreign package leaflet
    c. A Dutch or English authorised translation of the **complete** foreign package leaflet, if the package leaflet is drafted in a language other than Dutch, English, French or German. A translation only of the amended section(s) will not suffice.
4. In addition, the other obligations to provide information, as stipulated under section 2 of this policy document, remain in force unaltered.

Variations in the foreign package leaflet will only be adopted in the Dutch package leaflet of the parallel product if this involves safety information or certain parallel-specific information (e.g. storage conditions) and following assessment by the MEB. Indications, dosage, method of use and administration will remain **unchanged** compared to the approved version for the withdrawn reference product. This is in line with Art. 48, section 2, of the Medicines Act. After all, the parallel product will not be linked to a new reference product.

As far as the chemical-pharmaceutical particulars are concerned, the assessment by the authorisation authority in the country of origin will always be followed.

4. Obligations regarding pharmacovigilance

4.1 Reporting adverse reactions

The parallel authorisation holder may gain access to information about suspected adverse reactions related to the parallel product for which the authorisation holder has a parallel marketing authorisation. The parallel authorisation holder is obliged to report these adverse reactions as soon as possible, but in any event within fifteen days, to the Netherlands Pharmacovigilance Centre Lareb.

Lareb will process and submit reports of suspected adverse reactions which fulfil the requirements for reporting to EudraVigilance. If a parallel authorisation holder has procedures/systems for processing suspected adverse reactions itself and reporting these to EudraVigilance, the notification relating to the parallel product does not need to be sent to Lareb. The notification can then be reported directly to EudraVigilance. The original authorisation holder in the country of origin and the marketing authorisation holder of the Dutch reference product can access the notification via EudraVigilance.

The original authorisation holder is responsible for the pharmacovigilance system and the appointment of a 'Qualified Person for Pharmacovigilance' (QPPV). The parallel authorisation holder does not have any obligation in this respect. In line with the EMA Q&A document (Electronic submission of Article 57(2) data, version 1.11, July 2017) it is not obligatory in the Netherlands for the parallel authorisation holder to add details about the parallel products to the 'Extended EudraVigilance Medicinal Product Dictionary (XEVMPD)'. If the authorisation holder for the Dutch reference product or the original authorisation holder in the country of origin requires any additional information regarding pharmacovigilance, the parallel importer must honour this request.

4.2 Reporting quality defects

Suppliers/authorisation holders of medicinal products, including parallel importers, must report any quality defects in medicinal products to the MEB and the new Dutch Health and Youth Care Inspectorate (IGJ). For more information, please refer to the IGJ.