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Human Medicines Evaluation

Recommendations for the implementation of the exemptions to the labelling and package leaflet obligations in the centralised procedure

Quality Review of Documents (QRD) Group

1. Background

Following the revision of the pharmacovigilance legislation in 2012 the scope of Article 63(3) of Directive 2001/83/EC has been expanded to cases where the product is not to be delivered directly to the patient or where there are availability issues:

'Where the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health,

- *grant an exemption to the obligation that certain particulars should appear on the labelling [immediate and/or outer] and in the package leaflet.*
- *They may also grant a full or partial exemption to the obligation that the labelling [immediate and/or outer] and the package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.'*

Also, in accordance to recital 31 of Directive 2010/84/EU, it is possible to deviate from the requirements for labelling and packaging in order to address **severe availability problems** related to the potential lack of:

- **authorised medicinal products** (e.g. centralised products not marketed in certain Member States), or
- **medicinal products placed on the market** or **shortages** thereof (e.g. marketed products which become unavailable for a limited period of time due to manufacturing reasons).

***Rev.4 Changes since the last revision:** Clarifications on which labelling components are covered by Art.63 (update of sections 2.1 and 2.2), moving of information from section 3.3 as well as information on shortage from section 3.1 to section 2.2 and addition of more flexibility with regards to omission of particulars requests under Art.63.3 affecting small MSs where multilingual packs are used.



The provisions related to exemptions for orphan medicinal products remain the same, as per Article 63(1) of Directive 2001/83/EC:

'In the case of certain orphan medicinal products, the particulars listed in Article 54 may, on reasoned request, appear in only one of the official languages of the Community'.

Table 1. Overview of Article 63 of Directive 2001/83/EC, as amended in 2012

Article	Certain orphan products	Product not to be delivered directly to the patient	Severe availability problems
Art. 63(1) Particulars listed in Art 54 to appear in only one of the official languages	Art 54. - Labelling (outer packaging or immediate packaging, if no outer packaging)	N/A	N/A
Art. 63(3) Exemption to the obligation that certain particulars appear on the labelling and patient leaflet	N/A	Labelling (outer and/or immediate) Package leaflet	Labelling (outer and/or immediate) Package leaflet
Art. 63(3) Full or partial exemption to the translation into the official language(s) for the labelling and patient leaflet	N/A	Labelling (outer and/or immediate) Package leaflet	Labelling (outer and/or immediate) Package leaflet

The present document has been developed by the European Medicines Agency, via the Quality Review of Documents (QRD) , taking into account the experience gained when reviewing exemption requests for centralised products under Article 63 since 2008.

Its aim is to present the principles for the handling of the exemptions to the labelling and package leaflet obligations.

2. Principles agreed for granting exemptions to the labelling and package leaflet obligations in the centralised procedure

Blue-Box requirements do not fall under the scope of Art.63 exemption requests.

In case the conditions based on which an exemption was granted no longer apply (e.g. no longer "*not intended to be delivered directly to the patient*", loss of orphan designation), the labelling exemption granted by the QRD Group will be re-assessed by the Group on a case-by case basis.

2.1. Orphan medicinal products [Article 63 (1)]

- The request for a translation exemption affecting outer packaging should be submitted and reviewed by the QRD group. The group will also review requests for translation exemptions in accordance with Art. 63(3) (see section 2.2) affecting the immediate labelling and the package leaflet when these are submitted together with a request affecting the outer labelling.
- The use of more than one language may be accepted by the QRD group, as per previous cases.

- In case the QRD group grants the exemption, it will only be applicable for the printed materials. Annexes IIIA (labelling) or IIIB (package leaflet) will still be translated in all EU official languages and published on the EMA website (see section 3.4).
- The outcome of the QRD group decision will be reflected in the CHMP assessment report and in the EPAR published on EMA website. (for requests made as part of a regulatory procedure) and in the QRD table of decisions (see sections 3.3 and 3.4).
- In cases where one or more Member States oppose the request, advice from the European Commission will be sought.
- The validity of the exemption granted in the pre-authorisation phase is subject to the COMP confirmation of the maintenance of orphan designation after CHMP opinion and endorsement by the European Commission.

2.2. Medicinal products not intended to be delivered directly to patients or severe problems in the availability of the medicinal product [Article 63(3)]

Exemption to the obligation that certain particulars should appear on the labelling (outer and immediate) and in the package leaflet:

- Requests for omission of particulars for medicinal products not intended to be delivered directly to patients or in case of severe availability problems related to the potential lack of authorised medicinal products or of medicinal products not being marketed, should be submitted to and reviewed by the QRD group (Figure 1).

In case the QRD group grants the exemption, it will only be applicable for the printed materials. All linguistic versions will contain the same information and the elements to be omitted will appear **grey-shaded** in annexes IIIA (labelling) and IIIB (package leaflet).

- In exceptional cases, requests for omission of particulars with the aim to create multilingual packages could be granted only for those Member States intending to use multilingual packages, e.g. where severe availability problems only exist in a limited number of Member States and when a consensus within the QRD group cannot be reached.

Only the relevant linguistic version(s) will reflect the elements to be omitted in **grey-shading** in Annexes IIIA (labelling) and/or IIIB (package leaflet). In case of disagreement between MSs sharing the same language, the linguistic version in question will contain clarification notes to indicate for which country this omission is applicable.

- The QRD recommendations on exemption requests should be adopted by the CHMP. The outcome of the QRD group decision will be reflected in the EPAR published on EMA website (for requests made as part of a regulatory procedure) as well as in the QRD table of decisions (see sections 3.3 and 3.4).
- Requests for omission of particulars for medicinal products in case of severe availability problems related to shortages will be addressed in a different process since the acceptability thereof will be very much linked to the review of the actual shortage situation. Therefore, the review of exemption requests in case of shortages should be a matter of national recommendation. This type of exemption shall be processed by the parties involved in the evaluation of the shortage, rather than by the QRD group (Figure 1):

- The Marketing Authorisation Holder (MAH) should consult the concerned Member State in the context of the assessment of the exemption, and according to their national procedures;
- Since the outcome of the assessment will be provided to the EMA, the QRD secretariat should inform the QRD group accordingly (either at the plenary meetings or by written procedure). This would allow keeping track of what types of requests are approved, which may help to further develop criteria in the future.

Exemption to the translation obligation of labelling (outer and immediate labelling) and package leaflet:

- The request for a translation exemption should be handled at national level, even if it concerns all Member States.
- The request may refer to all labelling components and package leaflet (full exemption) or to one of the labelling components and/or package leaflet (partial exemption).
- The relevant national decision will not be published on the EMA website: it will not be reflected in the assessment report, since the CHMP's approval will not be required, and will not be included in the QRD table of decisions.

2.3. Generic/hybrid products

Design, layout and type of container are key elements when considering a labelling exemption request. Therefore, requests for exemptions of particulars or translation exemptions for generic/hybrid products will not be granted automatically, even if a similar request has already been accepted for the originator product. A separate request will have to be submitted and considered according to the process described in this document.

3. Revised review process

3.1. Handling of the review of the exemption requests

The information to provide as part of the requests related to the exemption obligations can be found in Annex 1.

The exemptions related to Art. 63(1) 'orphan medicinal products' and to Art. 63(3) 'omission of certain labelling requirements' will be discussed at the QRD plenary meetings. The requests related to the 'translations exemptions' as per Art. 63(3) will have to be addressed directly to the Member States. Please refer to the list of national contact details published on EMA website:

https://www.ema.europa.eu/documents/other/list-details-national-competent-authority-contact-requests-translation-exemption-falling-under/83/ec-cases-shortages_en.pdf

Moreover, in cases where an urgent review is required, the option of a **written procedure** for certain exemptions will be considered. The outcome of the exemption requests reviewed via written procedure should also be shared with the QRD group at the plenary meetings, to help building up experience.

A detailed process map highlighting the current process and the addition of a written procedure together with the steps related to the publication of further information regarding the decisions on the exemption requests can be found in Annex 2 (Figure 1).

Based on the conclusion regarding the exemptions related to severe availability problems in the case of shortages, the review of such exemption should be handled by the national competent authorities.

3.2. Timing

- For new marketing authorisation applications, all exemption requests handled by the QRD group should be submitted at the earliest at the time of submission of the Marketing Authorisation Application and at the latest when submitting the responses to Day 180 LoOIs or D90 LoQs in case of an accelerated procedure.
- For the review of requests at the QRD plenary meetings, the QRD group should receive the information at least **4 weeks** prior to the meeting. For the review of the requests to be handled by written procedure, the QRD group will need 28 calendar days (**4 weeks**) to review them. This timetable might need to be revised in case of urgent requests, where the availability problem could lead to an out of stock situation, e.g. in small Member States.
- For shortage situations, timelines will be agreed on a case-by-case basis with the Member State(s) concerned.
- The MAH should liaise with the relevant Member State(s) for the timing for submission of exemption requests handled at national level.

3.3. Transparency of the review process

Any decisions on the exemptions taken by the QRD group should be published on the **EMA website**. This will be done through the publication of a compilation table with the QRD decisions once the regulatory procedure is finalised. As translation exemptions (Art. 63(3)) are taken at national level and shortages would only be temporary exemptions, these will not be reflected on the EMA website.

3.4. Exemption requests in the post-authorisation phase

The requests related to the omission of particulars in the labelling and package leaflet (Art. 63(3)), as well as translation exemption requests of orphan medicinal products (Art. 63(1)), received post-authorisation, should be submitted for assessment by the QRD Group, ideally, as part of a regulatory procedure. The decision as to which procedure should be used will be made on a case-by-case basis.

The requests related to the translation exemptions and shortages (Art. 63(3)), received post-authorisation should be submitted directly to the Member States as explained in the previous sections.

Annex 1 - Information to be provided as part of the exemption request

Applicants are advised to provide the following information:

- A detailed and comprehensive request justifying why it is not possible to market the product with the labelling and package leaflet information in the language(s) of the Member State(s) concerned or with the full particulars of the labelling and package leaflet. This should include detailed figures for aspects such as manufacturing issues, production volumes/forecasts, estimated number of patients treated per country (prevalence of the disease), distribution vs. cost implications for the applicant, information on language(s) to be used, handling of the medicine by the users etc.
- To specify exactly which components of the labelling will be affected. In addition, the applicant should explain how, in their view, the product will still be able to be distributed, stored, administered/used correctly and safely, when certain information is not to be provided at all or will be provided in a language(s) different than the one of the Member State(s) concerned.
- To submit the proposed mock-ups for the labelling components to be placed on the markets concerned, when applicable.
- In addition to the above, for translation exemption requests as per Art. 63(3) handled at national level, the latest version of the product information available, as well as the outcome of any other exemption request handled by QRD Group, should be provided. Please liaise with the relevant Member State(s) for the full list of documents to provide for this national request.

Annex 2 – Handling of exemption requests summary

Figure 1. Handling of exemption requests either at the QRD plenary meetings, by written procedure or at national level.

