EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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 and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling 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).

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*'.

***Rev.3 Changes since the last revision:** Timing of submission of exemptions as per Art.63(1) and Art.63(3); clarifications on information to be submitted to NCAs when submitting a translation exemption at national level under Art.63(3); clarification on validity of exemptions granted as per Art.63(1) in the pre-authorisation phase.

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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 Package leaflet	Labelling (New) Package leaflet (New)
Art. 63(3) Full or partial exemption to the translation into the official language(s) for the labelling and patient leaflet	N/A	Labelling (New) Package leaflet (New – partial exemption)	Labelling (New) Package leaflet (New)

The European Medicines Agency, via the Quality Review of Documents (QRD) Group, had already gained some experience reviewing exemption requests for centralised products under Article 63 since 2008; a review process was already in place to evaluate such exemption requests. The QRD group has worked on a proposal to implement the new provision and has also revised the current process to accommodate the new scope.

This document aims 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

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

- The request should be submitted for discussion and review by the QRD group.
- 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 (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 and in the package leaflet:

- The requests should be submitted for discussion and review by the QRD group.
- 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).
- The outcome of the QRD group decision will be reflected in the CHMP assessment report (for requests made as part of a regulatory procedure) and in the QRD table of decisions (see sections 3.3 and 3.4).

Exemption to the translation obligation:

- The request for a translation exemption should be handled at national level, even if it concerns all Member States.
- 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.

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 rest of the Member States during the QRD 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, 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 remains linked to the overall assessment of the shortage situations and consequently the acceptability of the requests should be a matter of national recommendation.

This type of exemptions should be processed by the parties involved in the evaluation of the shortage, rather than by the QRD group (Figure 1):

- The concerned Member State should be consulted by the Marketing Authorisation Holder (MAH) 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.

Requests for omission of particulars in case of severe 'availability problems' related to authorised medicinal products not being marketed should be reviewed by the QRD Group (Figure 1).

3.2. Timing

- For new marketing authorisation applications, all exemption requests (handled either by the QRD Group or by the National Competent Authorities) 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.
- For the review of requests at the QRD plenary meetings, the QRD members 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 members 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, i.e. in small MSs.
- For shortage situations, timelines will be agreed on a case-by-case basis with the Member State(s) concerned.

Information about the data to be provided as part of the exemption request can be found in Annex 1.

3.3. Adoption by the Committee for Medicinal Products for Human Use (CHMP) of the QRD recommendation on the exemption request

The QRD recommendations on exemption requests should be adopted by the CHMP.

3.4. Transparency of the review process

- For the omission of certain labelling or package leaflet particulars, the omitted elements will appear grey-shaded in annex IIIA (labelling) and/or annex IIIB (package leaflet); this will indicate which particulars will not appear on the printed materials.
- For reviews of labelling or package leaflet exemptions linked to a regulatory procedure (e.g. new MAAs/line extensions), the granted exemption will be reflected in the **assessment report**.
- 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, they are not reflected on the EMA website.

3.5. Exemption requests in the post-authorisation phase

The requests related to the omission of particulars in the labelling and package leaflet received post-authorisation, should ideally be submitted 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) should be submitted directly to the Member States as explained in the previous sections.

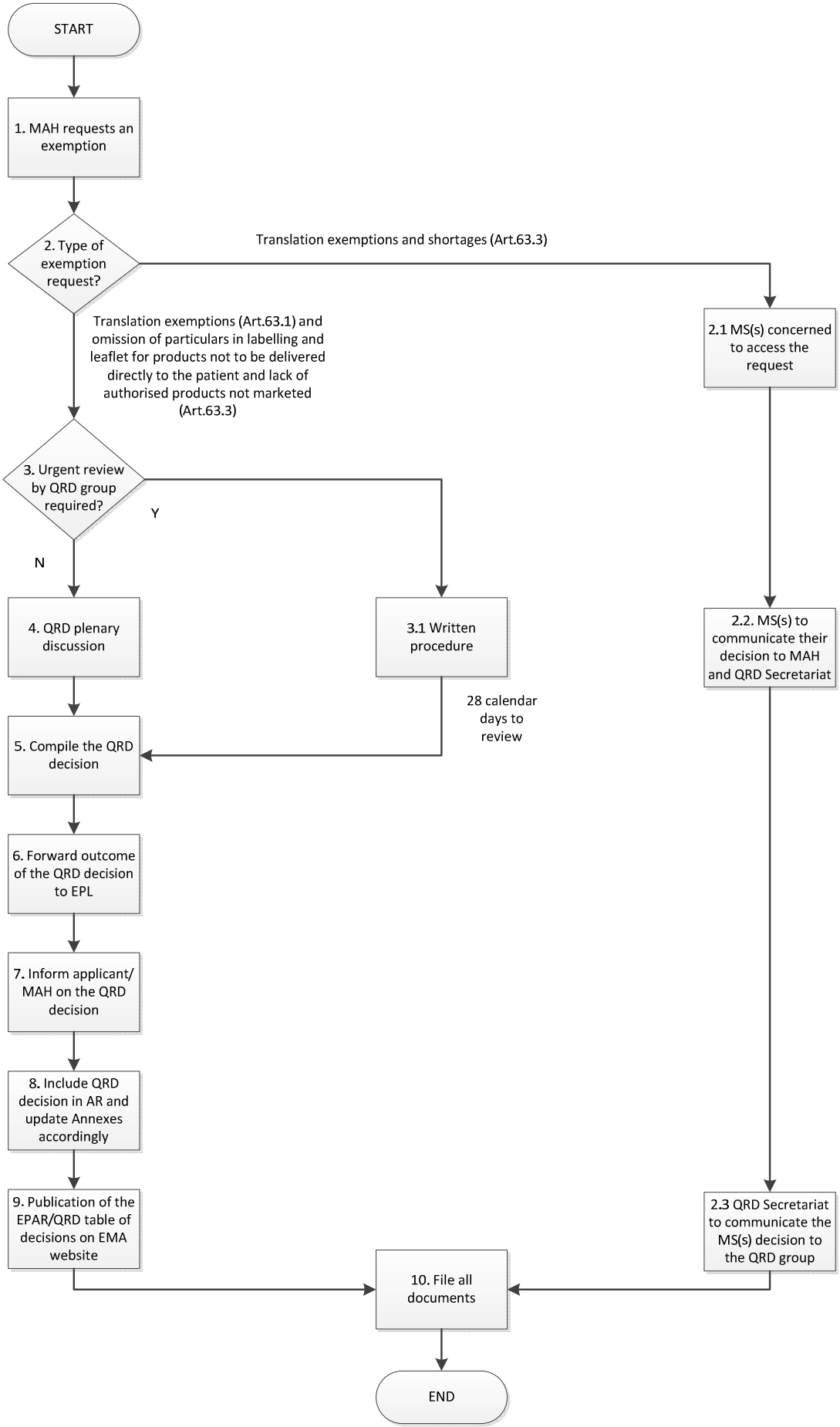
Annex 1 - Information to be provided as part of the exemption request

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.


START
1. MAH requests an exemption
2. Type of exemption request?
Translation exemptions and shortages (Art.63.3)
Translation exemptions (Art.63.1) and omission of particulars in labelling and leaflet for products not to be delivered directly to the patient and lack of authorised products not marketed (Art.63.3)
2.1 MS(s) concerned to access the request
3. Urgent review by QRD group required?
Y
N
4. QRD plenary discussion
3.1 Written procedure
28 calendar days to review
2.2. MS(s) to communicate their decision to MAH and QRD Secretariat
5. Compile the QRD decision
6. Forward outcome of the QRD decision to EPL
7. Inform applicant/ MAH on the QRD decision
8. Include QRD decision in AR and update Annexes accordingly
9. Publication of the EPAR/QRD table of decisions on EMA website
2.3 QRD Secretariat to communicate the MS(s) decision to the QRD group
10. File all documents
END