Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

URGENT SAFETY RESTRICTION
MEMBER STATE STANDARD OPERATING PROCEDURE

June 2000
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This document was produced by the CMD(h) in order to facilitate and harmonise the practical application of the urgent safety restriction procedure referenced in Article 3 (5) of Commission Regulation (EC) No. 1084/2003 effective 1 October 2003 by national authorities.

Prerequisite

1. EXTRACTS FROM EUROPEAN LEGISLATION: COMMISION REGULATION (EC) NO. 1084/2003.

Article 3 (5), *"Urgent Safety Restriction"*

"Urgent safety restriction" means an interim change to the product information concerning particularly one or more of the following items in the summary of product characteristics, the indications, posology, contra-indications, warnings, target species and withdrawal periods due to new information having a bearing on the safe use of the medicinal product.

Article 9, Urgent Safety Restrictions

1. If the holder, in the event of risk to public or animal health, takes urgent safety restrictions, he/she shall forthwith inform the competent authorities thereof. If the competent authorities have not raised any objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed to have been accepted.

The urgent safety restriction shall be implemented within a timeframe, as agreed with the competent authorities.

The corresponding variation application reflecting the urgent safety restriction shall be submitted immediately and in any case not later than 15 days after the initiation of the urgent safety restriction, to the competent authorities for the application of the procedures set out in Article 6.

2. Where the competent authorities impose urgent safety restrictions on the holder, the holder shall be obliged to submit an application for a variation taking account of the safety restrictions imposed by the competent authorities.

The urgent safety restriction shall be implemented within a timeframe, as agreed with the competent authorities.

The corresponding variation application reflecting the urgent safety restriction, including appropriate documentation in support of the change, shall be submitted immediately and in any case not later than 15 days after the initiation of the urgent safety restriction to the competent authorities concerned for the application of the procedures set out in Article 6.

This paragraph is without prejudice to Article 36 of Directive 2001/83/EC and Article 40 of Directive 2001/82/EC.

2. OTHER REFERENCES

2.1. Guidelines for Competent Authorities and the Agency, chapter 3: Conduct of Pharmacovigilance for Medicinal Products Authorised through the Decentralised or Mutual Recognition Procedure (PART II - Volume 9A)

2.2. Guidelines for Competent Authorities and the Agency, chapter 4: Rapid Alert and Non-Urgent Information System in Pharmacovigilance (PART II - Volume 9A)

2.3. Guidelines for Competent Authorities and the Agency, chapter 1: Undertaking of Pharmacovigilance Activities (PART II – Volume 9A)

2.4. Guideline on the Handling of Direct Healthcare Professional Communications on the Safe and Effective Use of Medicinal Products for Human Use (Guidelines for MAHs and Competent Authorities on Pharmacovigilance Communication (Part IV – Volume 9A)

USUAL PROCEDURE

3. BEFORE THE URGENT SAFETY RESTRICTION (USR) PROCEDURE IS INITIATED

The 24-hour USR procedure is triggered in the event of risk to public health. It may be initiated:
- on request of an MAH
- on request of a Member State-

When requested by an MAH, the need for a USR compared to an expedited Type II variation procedure should be discussed with the Reference Member State (RMS) as soon as possible and prior to initiation of the USR.

3.1. INITIATION PHASE

This phase allows for preparation of an assessment report and any communication documents required in order to ensure the smooth progress of the USR. The duration of the initiation phase depends on the complexity of the issue(s) to be managed. Safety issues resulting in a USR will normally be referred to the Pharmacovigilance Working Party (PhVWP) for discussion, where possible.

A) Urgent Safety Restriction (USR) at the request of the Marketing Authorisation Holder (MAH)

If an USR procedure is triggered by the MAH, the MAH should inform the national competent authorities (where a marketing authorisation was granted or is pending), without delay that provisional urgent safety restrictions will be taken due to a risk to public health.

- Before submitting the USR application, the MAH is advised to contact the Reference Member State (RMS) in order to prepare the documents, especially the revised summary of product characteristics (SPC), package leaflet (PL) if applicable and the draft Dear Healthcare Professional Communication (DHPC).
  When appropriate, a telephone/video conference or a meeting with the MAH and the RMS may be organized without delay.

- Before the start of the 24-hour period, the MAH should, without delay, send all available information by e-mail to the RMS as co-ordinator of the procedure. The RMS should then proceed with the USR pre-submission phase as outlined in Section 3.2.

B) Urgent Safety Restriction (USR) at the request of a Member State (MS)

If an USR procedure is triggered by a MS, the national competent authorities are advised to reach a consensus on the evaluation of the risk to public health and the urgency of the matter before start of the 24-hour period. Safety issues resulting in an USR will normally be referred to the Pharmacovigilance Working Party (PhVWP) for discussion, where possible.

Initiation by the RMS

If the RMS considers that an USR should be imposed on the MAH for a given medicinal product, it should inform without delay:

- All CMS through the Rapid Alert and MRVE mailboxes. All available information should be included and the same documents shall be sent to both mailboxes.
- The MAH by telephone initially, followed by email notification. When appropriate, a telephone/video conference, or a meeting with the MAH may be organised without delay. The MAH is responsible for informing its affiliates.

Initiation by a CMS

If a CMS considers that an USR should be imposed on the MAH, the following action should be taken before the start of the 24-hour period:

- The CMS should contact the RMS and all concerned member states without delay through the Rapid Alert and MRVE mailboxes. All available information should be included.
- If the RMS and CMS are in agreement that an USR is necessary, the RMS should take responsibility for subsequently co-ordinating the USR.
- The RMS should proceed without delay to inform the MAH by telephone/email of the need for an USR as agreed by the MS. When appropriate, a telephone/video conference, or a meeting with the MAH may be organised.
- The pre-submission phase described in Section 3.2 should then be followed by the RMS.

  If the MAH does not agree with the RMS and CMS that an USR is necessary, the RMS may in any case proceed with the USR as described in Section 3.2 following a specified time period for discussion (as appropriate). When appropriate, a telephone/video conference, or a meeting with the MAH may be organised without delay.

Note: if, in exceptional cases, a consensus cannot be reached between Member States, the matter could be considered by the Pharmacovigilance Working Party (PhVWP). If needed, an additional meeting may be organised by the PhVWP.
If a consensus cannot be reached, urgent national actions may be imposed on the MAH until the following type II variation procedure is finalised, e.g. DHPC, public statement. The MAH should be advised that agreement on the need for a 24-hour USR has not been reached between MS and that MS may take independent action. The MAH should be informed of any proposed communication to interested parties, and where possible should be provided with copies of the documents prior to their issue.

3.2. PRE-SUBMISSION PHASE

The purpose of the pre-submission phase is to reach agreement between MS and MAH on any proposals for amendments to the SPC and PL (if applicable), content of the DHPC with any draft communication texts, timetable for submission and start of the USR and release of public communication, as appropriate. The smooth progress of the 24-hour USR period is facilitated if any issues are resolved within this pre-submission phase i.e. prior to actual submission of the USR. To assist this, the RMS will circulate a preliminary assessment report to MS and the MAH.

The pre-submission phase is not intended to replace the 24-hour USR procedure. It may not be possible or appropriate for some issues to include a pre-submission phase, or it may not be possible to reach agreement on all aspects of the USR prior to the formal initiation. In such cases the 24-hour USR procedure should immediately follow the initiation phase.

The pre-submission procedure to be followed is outlined below:

All available information concerning the USR should be sent to all Member States contact points, whether concerned or not, via the Rapid Alert and MRVE mailboxes and by email to the MAH.

- RMS prepares a preliminary assessment report and circulates this to MS and MAH for information. Draft proposals for the following information are included in the report, if available/appropriate.

- SPC amendments
- PL amendments
- DHPC (contents and the proposed receiver of the letter)
- any draft communication texts e.g. public statements, Q&A documents etc.
- timetable for start and finish of the 24-hour USR
- timing for release of public communication
- deadline for comments on the preliminary assessment report and draft proposals
- proposals for actions relating to recall and distribution of new packaging information and distribution of DHPC together with corresponding timelines.

- The RMS may discuss any comments raised with the CMS and the MAH as appropriate.

- The RMS takes into consideration comments arising from the preliminary assessment report and updates any USR information as appropriate. This updated information is used as a basis for the 24-hour USR procedure (see Section 4).

- The MAH submits by email without delay, the completed USR procedure submission form (see Annex 1) and all updated documentation to the RMS in readiness for initiation of the 24-hour USR procedure.

A flow chart is provided in Annex 2.

4. 24-HOUR URGENT SAFETY RESTRICTION PROCEDURE

The RMS, as co-ordinator of the procedure, informs the CMS and the EMEA that the USR has been initiated and clearly defines the 24-hour period using UK Time.

The 24-hour period defined by the RMS should start during normal working hours. It would be preferable not to start an USR on a Friday or the day of, or before a public holiday in a MS.

The starting point of the 24-hour USR procedure is triggered by circulation by the RMS of the USR procedure form and associated information as follows.

The following text may be used as an example:

> *"You have received today the procedure form and a proposal for a revised SPC, PL (if applicable) and DHPC. You will find attached our assessment report on the USR. We kindly remind you that any major objection/comment should be sent to RMS, CMS and MAH within the next 24 hours, i.e. before … a.m./p.m., UK Time. Comments received after this period might not be considered."*

All information is circulated by the RMS via MRVE and Rapid Alert mailboxes between the MS/EMEA and by email to the MAH. Personal email addresses should not be used.

The following information as appropriate, should be circulated by the RMS simultaneously to the MS/EMEA/MAH:

- the completed USR procedure submission form (Annex 1)
- proposed revised SPC and package leaflet (if applicable)
- a DHPC (if applicable)
- a proposal for actions relating to recall and distribution of the new packaging information and distribution of DHPC together with corresponding timelines
- a proposal for timing of release of public communication
- an Investigator's Letter (if applicable for clinical trials)
- the timetable for the 24-hour USR
- the preliminary assessment report of the USR
- any draft communication texts
- any other relevant information relating to the matter in question

CMS should, without delay, confirm receipt of the USR information to the RMS.
The RMS informs the CMS that if no objection is received within the 24-hour period, the urgent safety restriction will be introduced.

CMS should send objections/comments if any to the RMS and other CMS. The comments raised by CMS should be focused on issues, which should be addressed immediately because of public health concerns, since other comments could be discussed during the forthcoming Type II variation procedure.

The RMS is responsible for liaising with the CMS and the MAH and for deciding whether the CMS comments are incorporated into the MAH's proposal of SPC/PL/DHPC. The interim version of the PL should be adopted within the timeframe of finalising the USR procedure. Note: the PL is finalised during the follow-up Type II variation.

5. AFTER THE 24-HOUR USR PROCEDURE HAS EXPIRED

The RMS should notify the MAH, all Member States (whether concerned or not) and the EMEA, of the final outcome of the USR at the end of the 24-hour procedure and that the USR should be introduced.

The final agreed version of the SPC and DHPC and if applicable, the package leaflet should be appended to the notification of outcome, and circulated via MRVE and Rapid Alert mailboxes, as appropriate.

The notification of outcome should include a statement concerning timely submission of the follow-up Type II variation, e.g:

- *For the above USR, the 24 hour period (date/h) has now expired.*
- *Regarding the proposed revised SPC and PL (if applicable), comments were received from... This has led to an amendment of section "…" / no comments were received*
- *Regarding the DHPC, comments were received from... This has led to an amendment of paragraph "…"/ no comments were received*

The MAH committed to submit a type II variation on "date" according to Article 9 of Commission Regulation* (EC) No. *1084/2003.*
Until this type II variation procedure is finalised, the attached SPC and PL (if applicable) should be considered as the current version.@
Attached SPC, PL (if applicable)

** **Note**:*
In any case, the proposed date of submission of the Type II variation should be not later than 15 days after initiation of the 24-hour USR procedure (an automatic validation procedure for Type IB variation is to be applied).

If applicable, the MAH commits to send the DHPC to an agreed target of healthcare professionals in each Member State within an agreed timeframe with the RMS and each individual CMS.

The MAH submits translations of the revised SPC, and DHPC, if applicable, to national authorities usually not later than 24 hours after completion of the 24-hours USR procedure and if applicable a proposal for a revised package leaflet.

National competent authorities may adopt an interim implementation in conformity with the revised SPC and PL.

The updated electronic version of the interim package leaflet should be made immediately available through the MS national network for management of external communications e.g. publication on the authorities' websites. This would be integral to the competent authorities national communication strategy. The package leaflet will be finalised during the follow-up type II variation.

Note: notwithstanding the procedure of the USR, national competent authorities:

- should consider whether it is appropriate to publish a national press release.
- can suspend/withdraw the marketing authorisation which has been granted following a mutual recognition or a community referral if they consider that it is necessary for the protection of public health (Article 36 of Directive 2001/83/EC) ; all Member States, the European Commission and the EMEA should be informed within 24 hours.
- can proceed to a recall, if appropriate (see Annex 3).

Following completion of the USR, in cases where public statements are made (DHPC, active or passive press

releases, publication on their website) authorities should consider sending early information (under embargo) to interested parties such as professional societies, pharmacovigilance centres and possibly patient groups who may need to prepare themselves for questions from health professionals and consumers.

List of abbreviations:

CMD(h): Co-ordination Group for Mutual Recognition and Decentralised Procedure-Human
USR: Urgent safety restriction
MAH: Marketing Authorisation Holder
MRP: Mutual Recognition Procedure
MS: Member State
RMS: Reference Member State
CMS: Concerned Member State
PhVWP: Pharmacovigilance Working Party
DHPC: Dear Healthcare Professional Communication
SPC: Summary of Products Characteristics
PL: Package Leaflet
EMEA: European Medicines Agency
Q&A: Questions and Answers

ANNEX 1

SUBMISSION FORM

URGENT SAFETY RESTRICTION PROCEDURE

Brief description Urgent Safety Issues identified:

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RMS

AT	☐	BE	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐	EL	☐
ES	☐	FI	☐	FR	☐	HU	☐	IE	☐	IS	☐	IT	☐	LI	☐
LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐	PT	☐
SE	☐	SI	☐	SK	☐	UK	☐								

CMS

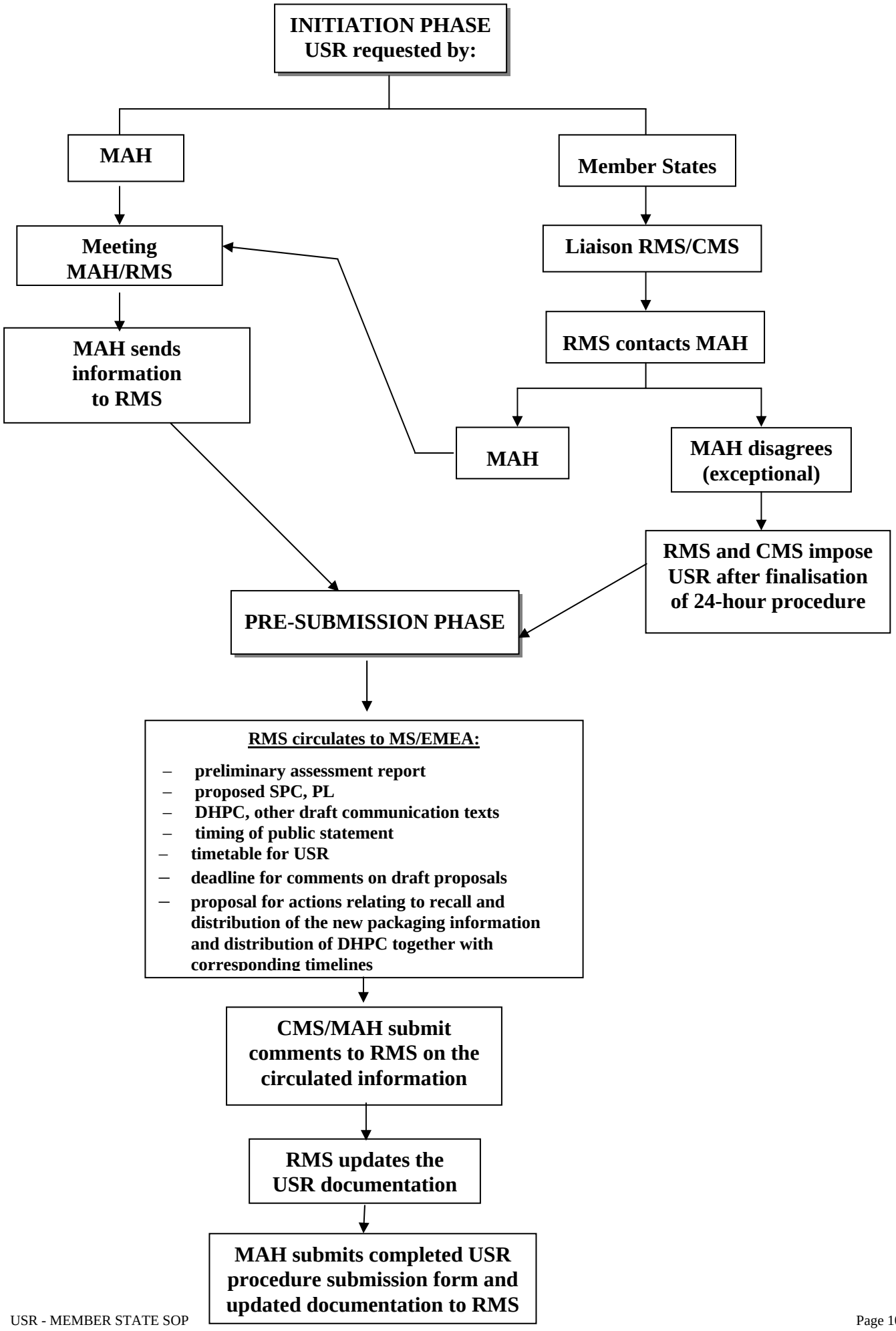
AT	☐	BE	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐	EL	☐
ES	☐	FI	☐	FR	☐	HU	☐	IE	☐	IS	☐	IT	☐	LI	☐
LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐	PT	☐
SE	☐	SI	☐	SK	☐	UK	☐								

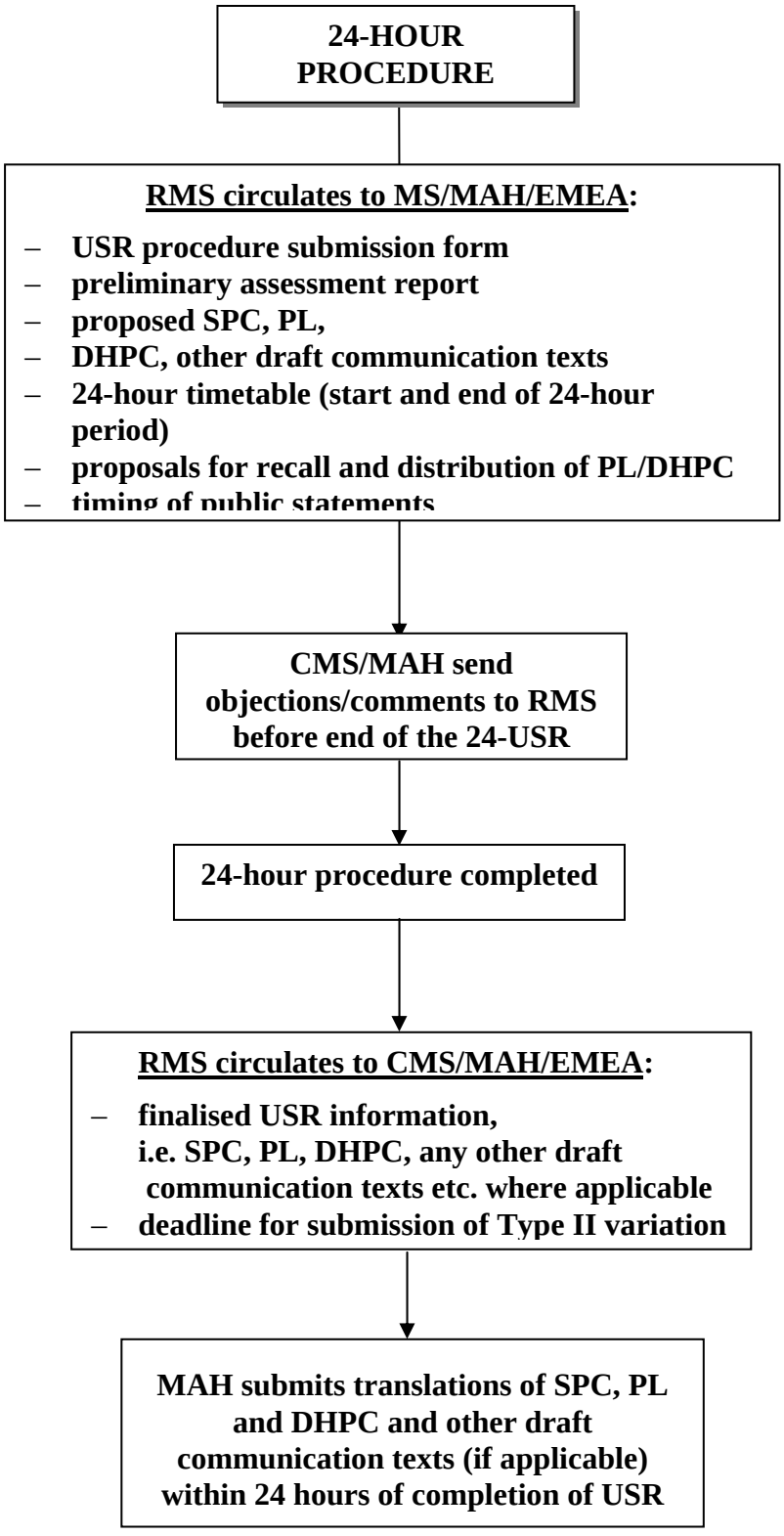
Product Name, if appropriate, Strength and Pharmaceutical Form	
MAH	
Procedure number	
Description of provisional urgent safety restriction to be taken:	

Documents attached:

- **Information related to Urgent Safety Issue**
- **Proposed revised SPC**
- **Proposed revised PL** ***(if applicable)***
- **Dear Healthcare Professional Communication, other draft communication texts** ***(if applicable)***
- **Investigator/s letter** ***(if applicable)***

ANNEX 2: FLOW CHART FOR THE USR PROCEDURE




24-HOUR PROCEDURE
RMS circulates to MS/MAH/EMEA:
– USR procedure submission form
– preliminary assessment report
– proposed SPC, PL,
– DHPC, other draft communication texts
– 24-hour timetable (start and end of 24-hour period)
– proposals for recall and distribution of PL/DHPC
– timing of public statements
CMS/MAH send objections/comments to RMS before end of the 24-USR
24-hour procedure completed
RMS circulates to CMS/MAH/EMEA:
– finalised USR information, i.e. SPC, PL, DHPC, any other draft communication texts etc. where applicable
– deadline for submission of Type II variation
MAH submits translations of SPC, PL and DHPC and other draft communication texts (if applicable) within 24 hours of completion of USR

ANNEX 3: FORM FOR USE IN AGREEING TIMESCALES FOR REVISED INTERIM PL AND/OR PRODUCT RECALL (AS APPLICABLE)

Section 1: FOR RMS TO AGREE WITH MAH AT TIME 0 OF USR

Is USR likely to result in important changes to PL or packaging?

- Yes
- No

Does public health impact of changes warrant:

- Immediate recall and repackaging?
- Phased approach?

Overall timescale of implementation of changes <u>in all MS</u>:

- Deadline for availability of new PL/package insert to patients:
- Deadline for revised PL/package insert to be used in all newly manufactured stock:

Section 2: FOR NATIONAL AGREEMENT WITH MAH

Fate of current stock:				
Company warehouse	**Embargo**	**Y**	**N**	**Current stock :** **Date of Embargo :**
	Repack	**Y**	**N**	*Date of repack :*
Wholesaler	**Recall**	**Y**	**N**	**Current stock :** **Date of recall :**
Pharmacy	**Recall**	**Y**	**N**	**Current stock :** **Date of recall :**

Specific local arrangements if necessary (eg provision of new PILs at retail level to be handed over when product is dispensed)