

Position Paper

Reference safety information: challenges to the generic industry due to labelling harmonisation issues among different Member States

Date of release: 2020-05-08

Version: 01_FINAL

1. Executive summary

Key tool to communicate risks and assure the safe and effective use of medicinal products is Product Information (PI) i.e. Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL).

Inconsistent PI is evident across the EU/EEA for the same active substance (INN), between countries but also within one country, especially for older products registered via different national authorization procedures or having different reference products.

Main scope of this position paper is to address the need to align PI for the same INN across the EU, providing the same and most recent information to HCPs and patients, and to further reduce complexity of variation process to be able to provide information timely and consistently, with the emphasis on generic products.

Several examples were given related to the complexity of the safety variations from the company process point of view, as well as from regulatory point of view:

- Regulators need to be aware that companies have different systems in place for implementation of updates to the PI defining core safety text or Reference Safety Information (RSI) first, which is then transferred to the PI (local labelling). Enough time should be given to companies to fulfil these internal processes.
- In general, safety variation complexity could be reduced focusing on two main areas; (1) **timetable** for variations should be adjusted for published corrections, class effect recommendations and late publications; (2) **proposed wording/PI content** coming from different regulatory procedures (PRAC signals, referrals, PSUSA etc) should be more detailed, combining more PI recommendations into one and fit to the existing text.

The PI update in generic companies is even more complex because it combines different sources and processes, which follow different timelines such as internal signal process, HA requests and reference PI updates. Furthermore, core safety text (RSI) should be established first so that any further PI updates across the EU could end up as harmonized text.

Medicines for Europe, therefore proposes a pilot project with CMDh and other industry association in which core safety text will be defined for selected products and aligned by consensus using most-up-to date core safety text available in the EU, as due to the different product backgrounds submitting variation and providing justification is difficult to achieve for proposed generic products. At start pilot could include molecules from HaRP initiative that do not have core safety text.

2. Abbreviations

ACO	Addendum to Clinical Overview
ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - human
CP	Centralised Procedure
CSP	Core Safety Profile
DCP	Decentralised Procedure
DRA/HA	Drug Regulatory Authority/ Health Authority
EEA	European Economic Area
EMA	European Medicines Agency
EN	English language (text)
EU	European Union
GSL	General sale list
HaRP	Harmonisation of RMP Project
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
INN	International non-proprietary name (of active substance)
MAH	Marketing Authorisation Holder
MRP	Mutual recognition procedure
MS	Member State
NP	National Procedure
OTC	Over-the-counter
P	Pharmacy Medicine
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Product Information
PIL	Patient Information Leaflet
POM	Prescription Only Medicine
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
QRD	Quality Review of Documents
RMS	Reference Member State
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
WEU	Well Established Use
WSP	Work Sharing Procedure

3. Scope

According to EU legislation, among others, objectives of pharmacovigilance are preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation, and promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals (HCP) and the public.¹

Product information (PI), i.e. Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) are key tools to communicate risks and assure the safe and effective use of medicinal products.

Therefore, main scope of this position paper is to address need to align product information for the same INN across the EU/EEA (hereinafter referred to as EU), providing the most recent information to HCPs and patients, and to further reduce complexity of variation process to be able to provide information timely, with the emphasis on generic products.

4. Background information

Inconsistent communication of safety information to HCPs and patients is evident across the EU for the same INN, between countries but also within one country, especially for older products registered via different national authorization procedures or having different reference products.

Medicines for Europe members standpoint is that this information should be aligned and updated with most recent information, giving the opportunity to have available most-up-to-date information to all HCPs and patients across the EU.

This core safety text or Reference Safety Information (RSI), referring to section 4.3. to 4.9. of the EU SmPC², should be aligned across the EU as much as possible, for the same INN used in the same target population. RSI contains relevant safety information which should be listed in all countries where the product is marketed. It is acknowledged that the local regulatory authority could specifically require a modification to the PI; however given that there is no rationale to consider population in the EU different from one country to another, there is no scientific rationale for different safety information/RSI in the EU, but only for historical and administrative reasons.

In addition RSI also serves as the internal company document, which is basis for regional/local labelling and for ensuring consistency of information between countries when a new risk has been identified and needs to be added to the local labelling. It is also the main company document for safety evaluation like signal

¹ GVP Annex I - Definitions (Rev 4), EMA/876333/2011, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf

² Guideline on Summary of Product Characteristics (SmPC), Revision 2, September 2009, available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

management, scientific literature assessment, Individual Case Safety Report (ICSR) evaluation, Adverse Drug Reaction (ADR) listedness and Periodic safety update reports (PSUR/PBRER/ACO) preparation.

RSI could be updated due to authority alerts (from the EU and non-EU), European harmonisation procedures, changes in reference SmPC or any other local/national labelling document and internal signal detection.

The RSI is a common area of non-compliance observed during inspections. These include critical deficiencies and major findings in safety data management and the management of RSI and failures and/or delays in submission of safety variation applications to update the safety sections of SmPCs and PILs in accordance with RSI.

In some companies, RSI is prepared based on centralised procedure (CP)/decentralised procedure (DCP)/mutual recognition procedure (MRP) SmPC and has a more comprehensive content, while in other companies the RSI is based on all available SmPCs and RSI ends-up in having minimum information available in all SmPCs. The most complicated are INNs for which a reference product no longer exists or for which there are different reference products SmPCs across the EU or stand-alone registrations, like Well-Established Use (WEU), ie products registered before current EU legislation with limited available source data corresponding with today's requirements and big differences between the markets.

Medicines for Europe also wants to raise awareness about the complexity of the variation process to update product information in general and especially when baseline product information (core safety text or RSI) is not aligned.

5. Challenges for generic Marketing Authorisation Holders (MAH) related to RSI and EU labelling update

The challenges to achieve harmonization of SmPC in the EU for the same INN can be divided as follows:

- Challenges regarding harmonisation and updating RSI
- Challenges regarding implementation of RSI changes to PI (SmPC/PIL) in the EU

5.1 Challenges regarding harmonisation and updating RSI based on internal safety signals and/or EU/national safety updates of reference SmPC are:

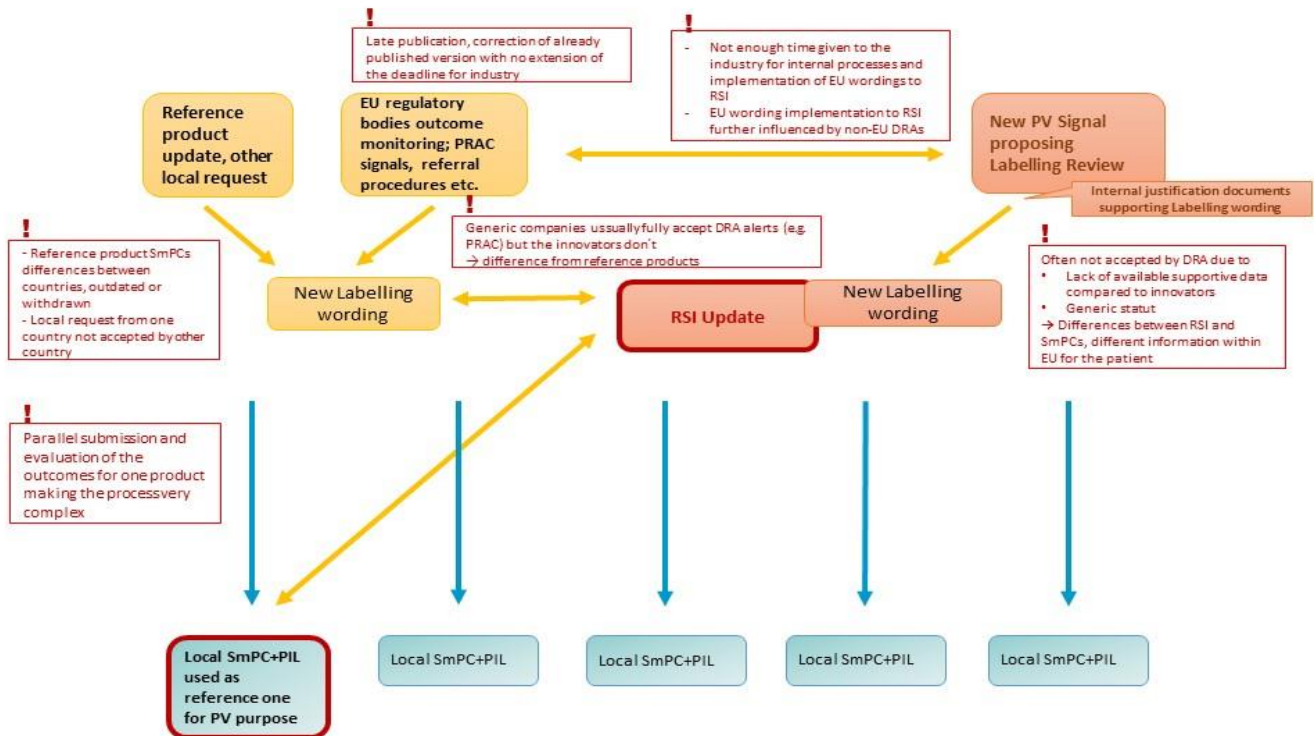
- Legal basis – generic versus stand-alone registration:
 - For standalone registration, like WEU, and fixed dose combination products less information may be available compared to innovator and local Drug Regulatory Authority (DRA) refuses the variation due to lack of sources (even if already approved for the INN innovators within EEA),
 - Internal signal outcomes are often not accepted by authorities; due to regulatory framework, generic companies are facing challenges in driving label changes resulting from internal signal management. Some of the DRA are not accepting the variations on the fact that innovator labels do not contain the proposed safety information. Thus the overall purpose of signal management applied for generic companies is questionable. This may create a scenario where the RSI contains the safety information but the SmPC/PIL would not,

- Difference in prescription status like P, POM, GSL, OTC could lead to different information across the Member states.
- Generic companies fully accept DRA alerts (e.g. PRAC signal outcomes and/or outcomes of referral procedures) and RSI is updated accordingly in a timely manner, but the SmPCs of the reference products are not updated, thus it leads to inconsistency in safety sections between generic and reference product for the same INN.
- When the RSI is based on SmPCs from national procedures good quality translation is necessary, otherwise the difference in the content or just in wording cannot be distinguished. This is time and source consuming.
- It is not clear how should generic companies proceed in RSI updates, when the reference product has been withdrawn from the market or non-marketed and thus not maintained.
- When product is registered in more countries, there is a possibility of national differences in the local SmPCs. Any such differences between RSI and SmPC can further be influenced by requirement of non-EU regulatory authorities.
- RSI preparation and subsequent implementation in the PI is in many cases not possible due to the short timelines for submission. PI has to be prepared in parallel to update of RSI. Please see the following examples where variation timelines impacted internal RSI update process:
 - Late publication of PSUSA on webpages (e.g. ebastine, see example in [Annex 1](#)),
 - Publication of corrected versions by agencies without extension of respective submission due dates (e.g. levofloxacin, see example in [Annex 1](#)).

Summary: It is acknowledged that RSI for the EU is the EU PI; however it should be taken into consideration that pharmaceutical companies are in most global companies that need core safety text (RSI) used for all territories to be able to coordinate different processes (signal detection, labelling changes, PSUR etc.). Regulators need to be aware that companies have different systems in place for implementation of updates to the RSI and SmPC (please see in [Annex 2](#)). Clear wording and enough time should be given to companies to fulfil these internal processes. The SmPC update process involves many activities starting with the trigger of new safety related information (internal signal, HA regulatory outcomes) and internal PV and Regulatory governance committees approval, subsequently regulatory dispatch preparation and timely submission to DRA, DRA approval and implementation on industrial level. Generally, processes of SmPC updates may follow different type of variations. The RSI update in generic companies is even more complex because it combines different sources and processes, which follow different timelines such as internal signal process, HA requests and reference SmPC updates.

Picture 1 shows complexity of workflow related to RSI and safety labelling updates.

Safety labelling changes and RSI – main challenges



Picture 1: Workflow of main challenges related to RSI and safety labelling updates

5.2 Challenges regarding implementation of RSI changes to PI (SmPC/PIL) in the EU and how to achieve harmonization of SmPC in the EU for the same INN are as follows:

- Often it is not possible to implement the RSI changes into local generic PI (the local reference product has different or outdated PI, limited available source data).
- Only minority of countries have in place database of SmPCs which allows easy monitoring or DRA sends request to generic companies after reference product update. In most of the countries the monitoring of reference products updates is complicated and time demanding and in some of the EU countries impossible, as those countries do not publish SmPCs.
- Reference product has been withdrawn and its PI is not updated anymore; at that point generic PI becomes most advanced. In that case it is not clear how to proceed in case of any variation or renewal; ie should generic PI still be compared with reference or should it only follow PSUSA/ PRAC update way forward.
- Challenges in Variations:

- In case of two or more DRA requests for PI safety changes in short time period, submission of new variation without approval of the last one is needed,
 - Submission of new variation is required in case of minor changes in the already agreed safety wording in the EU,
 - Some minor updates (other than side effects or precaution) may not be available for the reference product in all different MS. However, it will trigger Type II variation for generic despite the fact that nature of update is very minor.
- Unclear recommendations from DRA on how to implement changes to PI:
 - Should the similar content in the PI be deleted/updated or left unchanged,
 - In which section should the change be implemented,
 - Often the timetable and/or type of variation are missing.
 - During a Type IA some DRA make comments which are not relevant and unimportant, e.g. use just one space instead of two, missing full stop, use “x” instead of “x” (i.e. another type of “x”) for unit dose blister (30x1 tablet) etc. It is preferred to focus on the matter at hand, and the request to change these issues with the next update of the text.
 - In case of MRP/DCP variation some DRAs make corrections in texts after RMS approval.
 - The English (EN) common texts are considered to be the basis for the respective national translations. Therefore, they should not contain any information which is relevant only nationally, e.g. MA numbers, address of MAH etc. and DRAs should not require such things.
 - Request by individual authority to add adverse reaction in the labelling leads to additional inconsistencies. Such individual request should go thru PRAC signal to assure that signals are appropriately handled and avoid further labelling disharmonisation.

Summary: In general the basis for the PI update should be established first so that update across the EU could end up as harmonized text. It is very important that patient across the EU receive the same safety information for the same products (i.e same INN, dose formulation, target population) and in appropriate timelines. Consistent approach between DRAs is needed for RSI changes implementation.

Some examples of the above-mentioned challenges related to information update and implementation are listed in the table in [Annex 1](#).

6. Proposed solutions

The differences in content of RSI presents a great burden for MAHs and also for assessors. In addition, healthcare providers and patients receive inconsistent information across the EU related to same active substance, dose, formulation and indication. Therefore, we propose some possible solutions to have consistent information available for the same products across the EU:

- **For RSI content and updates:**

- The current EU SmPC format sections 4.3-4.9 should serve as an RSI ie, should be defined as reference information under the scope of safety variation. In order to have consistent information across EU, baseline safety information should be harmonised.
- The originator/innovator RSI should be made publicly available by the authorities to allow further updates for the products with the same INN without the need to submit further supporting data. Requests by individual authorities should be handled centrally through PRAC signal process to avoid inconsistencies.
- **For the aim to reduce variations complexity**, the following proposals are related to **variation timelines and labelling content/wording**:
 - Timetable for variations should be adjusted for published corrections, class effect recommendations and late publications.
 - Combining more PRAC recommendations into one if there is knowledge of ongoing parallel safety issues (PSUSA, signal detection) on the same INN or group of INNs.
 - The recommended wording should be more detailed (should a similar content in the PI be deleted/updated or not changed; where exactly in which section should the change be implemented).
 - The wording which is recommended should be based on previous versions concerning the same issue in the corresponding paragraphs.
 - Recommended wording which has to be rolled out to a complete INN group should be worded in a way that it also can be included to texts that are differently structured.
 - Implementation of DRA recommended wordings (e.g. safety alerts, referral outcomes) should be applied not only in generics but also in innovators PI.
 - Variation worksharing outcomes for safety labelling variations following company's signal detection should be made publicly available by the authorities to allow further updates for the products with the same INN without the need to submit further supporting data (alternatively also the MAH of other products containing same INN should be included into Type II variation worksharing allowing one outcome for the INN).
 - Authorities should timely publish the SmPC of the reference products to allow monitoring by generic companies and to send requests for update to generic MAH after approval of safety labelling update of the reference product.

Dialog between authorities and industry should continue to further enhance the variation process and achieve consistent approach between national competent authorities related to timelines and wording.

In addition, Medicines for Europe proposes a pilot project with CMDh in which core safety text will be defined for selected products and aligned by consensus using most-up-to date core safety text available in the EU, as due to the different product backgrounds submitting variation and providing justification is difficult to achieve for proposed generic products. Further details are provided below.

7. Worksharing (WS) proposal between Medicines for Europe and CMDh

Medicines for Europe identified candidate molecules for which the SmPC text could be further harmonized by regulators and industry, as products are approved via different procedures/having different references.

Proposed list concerns mature products with no reference product or different reference products across the EU (Please see [Annex 3](#)). MAHs are aware that there is an existing tool such as Art 30 which could trigger harmonisation. However, as the Art 30 referral is not appropriate for products with different reference products, Medicines for Europe believes that a model similar to RMP worksharing (HaRP - Harmonisation of RMP Project) could be agreed with CMDh for harmonization of sections 4.3-4.9 of the SmPC and corresponding sections in the leaflet. Moreover, proposed list concerns molecules already assessed in HaRP, and therefore considered as good candidates for RSI WS project start. HaRP project showed mutual agreement and excellent cooperation between CMDh and industry.

Medicines for Europe believes that it is essential to have harmonized PI across EU and to communicate appropriate safety information to HCPs and patients, and therefore invites other industry associations to participate in the future RSI worksharing.

Medicines for Europe proposes worksharing with CMDh in which the core safety text for these products will be aligned using most up-to-date PI available in the EU (as due to the different background, submitting a variation and providing justification is difficult for such generic products). Most recent information should be defined by CMDh/PRAC (or by consensus with MAHs), and all other PIs should be aligned with selected PI. As this WS concerns all products in the EU and different references, WS will allow arbitrary decision based on most recent PI approved by one authority and accepted by others.

After the final text of the PI is agreed, there should not be a need for individual variations and justification. The change should be implemented by MAH preferably with the next printing of the leaflet or within the designated timeline of 6 months. In that case, submission will refer to the arbitrary decision based on this WS and no further justification will need to be provided to the DRA for PI update.

Further WS flowchart should be discussed and agreed between authorities and MAHs.

Annex 1: Examples of challenges related to the safety PI updates and implementation (status from Jun/Sep 2019)

Challenges could be summarised as challenges related to timelines and related to content/labelling wording:

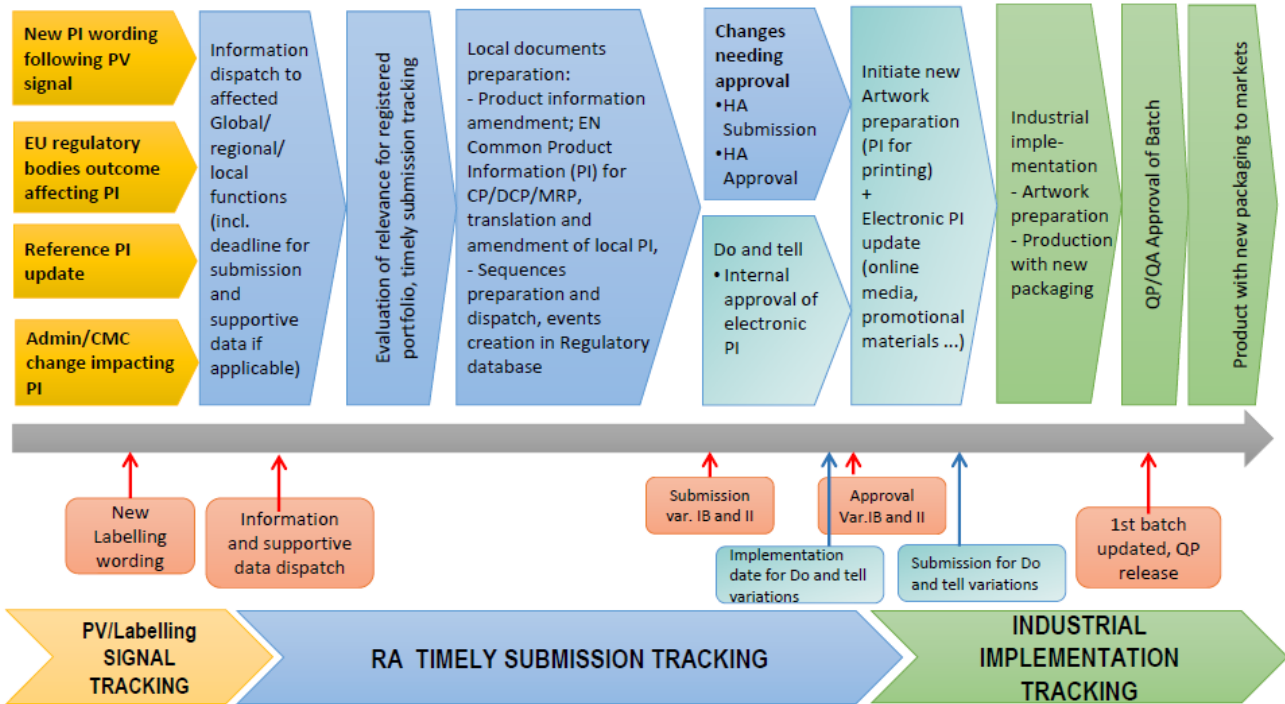
INN/Brand name	Issue	Issue details	Outcome
Amantadine, Minocycline, Paracetamol	Differences in safety related parts of the reference product because it is registered in NPs.	Different requests from national DRA during registration procedures	Differences in local SmPC and RSI in safety related parts for the same INN.
Diltiazem	Time inconsistency in different Drug Regulatory Agencies (DRA) for change Type II. DRA in Country 1 did not accept the combination of 2 procedures for the Type II change related to the same SmPC for the same product.	Country 1: The DRA partially accepted change in labelling (variation submitted in June 2017). During the ongoing procedure, new labelling information has been identified, but it could not be submitted, because Country 1 did not let the applicant know until the first variation procedure was concluded. Country 2: The procedure for type II variation is still ongoing (Type II variation submitted in Feb 2017).	Differences in local SmPC in safety related parts for the same INN and inconsistency between SmPCs and company's RSI.
Donepezil	Differences in safety related parts of the reference product because it is registered through DCP and national procedures (NPs).	In DCP variation, a DRA did not accept changes in line with the reference product from DCP as this has not been updated in the nationally registered reference product in that country.	Differences in local SmPC and RSI in safety related parts for the same INN.
Fentanyl transdermal patches	Variations for generic companies were required before reference labelling of originator was updated.	On 21 July 2016, the EMA completed a review of Durogesic. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there is a need to harmonise the prescribing information for Durogesic in the EU	Differences in safety related parts between reference and generic product, as update of reference was later than update of generic -> reference and generic labelling are different although

INN/Brand name	Issue	Issue details	Outcome
		(EMA/491912/2016). After this harmonization two further variations were required before reference labelling was updated: 1. CMDh/372/2018 (Feb. 2018) 2. PSUR Single Assessment PSUSA/00001370/201804 required by BfArM (April 2019).	there was a harmonisation in July 2016.
Ebastine	PSUSA/00001191/201805 has been published only 11 days prior to defined submission due date.	Publication of PSUSA on EMA webpage: 06 May 2019. Submission due date to agency stated in the PSUSA document: 15 May 2019.	It is not possible to wait for the RSI update and start common text preparation + coordinate the national text for all involved CMS afterwards within this short timeframe.
Fluoroquinolones	PRAC recommendation on signals (Signal of aortic aneurysm and dissection) from October 2018 and Article 31 referral for fluoroquinolone from March 14, 2019.	The first variation has not been approved and the second one has been submitted.	None of submitted variation has been approved.
Levofloxacin	PSUSA/00001854/201810 has been published in July 2019 and has been corrected by CMDh in August 2019 without an extension of submission due date.	Publication of PSUSA on EMA webpage: 11 Jul 2019. Submission due date to agency stated in the PSUSA document: 06 Sep 2019. Correction of CMDh position received on 13 Aug 19 via e-mail only (no publication on EMA webpage so far).	Common and national PI had to be corrected immediately. There is no time to wait for the updated RSI.
ACE-inhibitors (example Ramipril)	Multiple text changes concerning a similar or the same issue with recommended changes from different sources. They have to be rolled out to the whole group of INNs without considering that the recommended wording	CMDh meeting 25-27 Jan 2016 -Products containing Ramipril as monocomponent – proposed text: “mTOR inhibitors: An increased risk of angioedema is possible in patient taking concomitant medications such as mTor	Several variations had to be submitted to stay compliant. As the wordings are not always optimal, DRAs request changes with the consequence that depending on the countries included in

INN/Brand name	Issue	Issue details	Outcome
	<p>doesn't fit into the texts of other INNs of the group. The proposed wordings are often not based on each other (see details).</p> <p>Sometimes they are not well-considered (information got lost or spelling had been changed from one change to another). Nevertheless the variations have to be submitted as IA with an identical wording.</p>	<p>inhibitors (e.g. Temsirolimus, Everolimus, Sirolimus). Caution should be used when starting therapy."</p> <p>4 Apr 2016 EU PSUR WS SAR/CSP: "This risk may be increased in patients taking concomitant medications such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin."</p> <p>29 May 2019 CMDh October 2018 Report referring to PSUSA for cilazapril + hydrochlorothiazide: "Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor."</p> <p>May 2019: Comment from DRA to explain the abbreviation "mTOR" and therefore to add "(mammalian target of rapamycin)".</p>	<p>the procedure, the finally approved wording differ from the recommended wording and within the procedures of the same INN or INN group.</p>

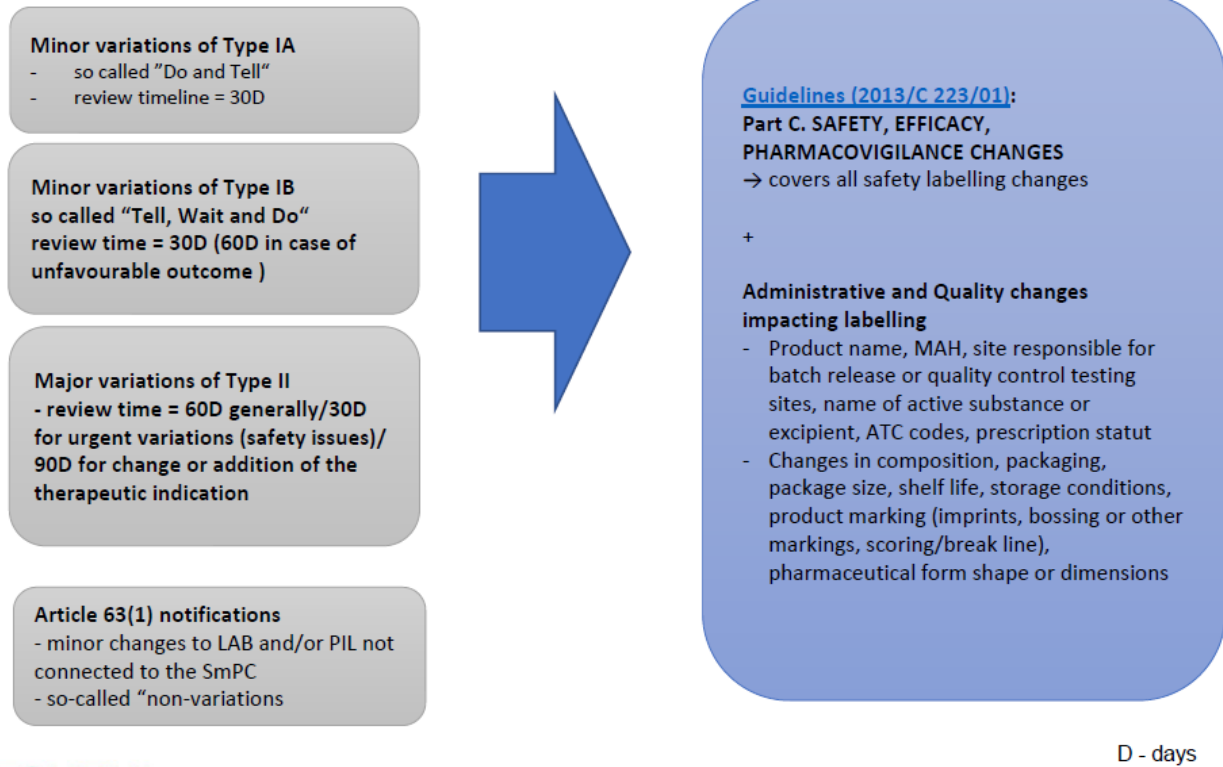
Annex 2: PI implementation schemes and legal obligation

Safety labelling (Product information) changes flow



Picture 2: PI changes scheme

EU variation types for labelling changes



Picture 3: Legal obligations – EU Variation types

EU regulatory bodies outcome impacting PI

- **CMDh – Co-ordination Group for Mutual Recognition and Decentralized procedures – human** on the website of Heads of Medicines Agencies (HMA)
 - **Agendas, Reports and Minutes for CMDh meetings**
 - **Public Assessment Reports** (Art. 45 and Art. 46 of the Paediatric regulation, Informal PSUR Work Sharing, PSUFU – PSUR follow-up procedures)
 - **Other, e.g.** CMDh recommendations and Relevant Q&A
- **EMA – European Medicines Agency**
 - **Agendas, Meeting highlights and Minutes from PRAC and CHMP meetings**
 - **Referrals (Art. 31, 107i, 20, 30)**
 - **PRAC recommendations on signals** (with national translations)
 - **PSUSA outcomes** (with national translations)
 - **EPARs**
 - **Other, eg.** Product information templates and guidelines linked to Labelling
- **EC- European Commission**
 - **Referrals, PSUSA** for products authorized via DCP/MRP/NP:
 - **PSUSA** for orig. authorised via CP

Usually more ongoing parallel safety issues (Periodic Safety Update Single Assessment - PSUSA, signal detection etc.) on the same INN or group of INNs. No coordination between outcomes, require almost daily monitoring of all the web pages necessary. National DRAs often coming with additional/different requests; reference products updates issued and published in parallel.

Picture 4: Legal obligations – EU safety procedures impacting PI

Annex 3: Proposed list of the INNs for harmonisation project

List of molecules already assessed as part of HaRP that could be candidates for the start of RSI WS

INN

Cineolum
Colchicine
Dienogest/ethinylestradiol
Diazepam
Diosminum
Ethosuximide
Fluorouracil (systemic use)
Hyoscine butylbromide
Melphalan
Menotrophin
Trospium chloride
Zolpidem

HaRP 1st wave in 2019, and 2nd wave in 2020, covered in total 32 molecules. Above listed molecules do not have Core Safety Profile published (https://www.bfarm.de/EN/Drugs/vigilance/PSURs/csp/_node.html), from the so-called European work sharing procedure (WSP). The WSP was initiated in 2002 with the aim of assessing PSURs regarding certain substances on a European level and to synchronise the basic statements in the product information of these substances. These molecules also do not have harmonized text thru CP registered products or Article 30 referrals.