Slovenská asociácia spoločností v oblasti liekovej regulácie
Slovak Association of Regulatory Affairs Professionals

Variation Regulation 1234/2008

Change as of Jan 2025

Modul 1

4. 6. 2024

COMMISSION REGULATION (EC) No 1234/2008

of 24 November 2008

concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

- Regulation & Annex
  - Definitions, Extension, Classification, Unforeseen var., Grouping, Elements to be submitted, 90-day assessment…
- Classification Guideline
  - Conditions
  - Documentation

Source: Consolidated TEXT: 32008R1234 — EN — 13.05.2021 (europa.eu)
EUR-Lex - 52013XC0802(04) - EN - EUR-Lex (europa.eu)

Usmernenia o podrobnostiach rôznych kategórií zmien, o výkone postupov stanovených v kapitolách II, IIa, III a IV nariadenia Komisie (ES) č. 1234/2008 z 24. novembra 2008 o preskúmaní zmien podmienok v povolení na uvedenie humánnych liekov a veterinárnych liekov na trh a o dokumentácii, ktorá sa má predkladať na základe týchto postupov

(2013/C 223/01)

Obsah

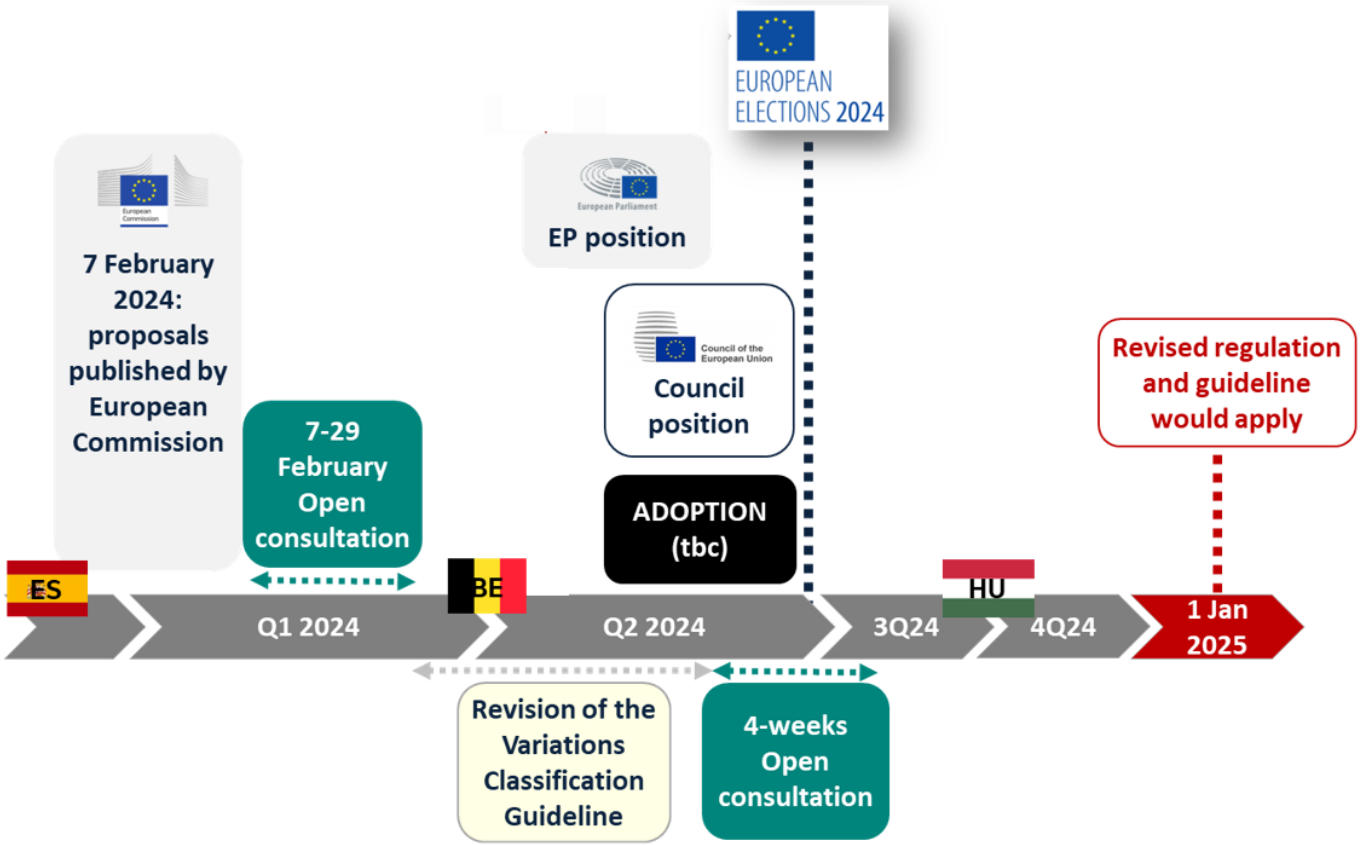
B.I.c.2. Zmena parametrov v špecifikáciách a/alebo minimálnych požiadaviek na špecifikáciu pre vnútorný obal účinnej látky	Podmienky, ktoré majú byť splnené	Dokumenty, ktoré majú byť predložené	Typ konania
a) Sprísnenie minimálnych požiadaviek na špecifikáciu	1, 2, 3, 4	1, 2	IA
b) Pridanie nového parametra do špecifikácií spolu so zodpovedajúcou skúšobnou metódou	1, 2, 5	1, 2, 3, 4, 6	IA
c) Vypustenie nevýznamného parametra v špecifikáciách (napr. vypustenie zastaraného parametra)	1, 2	1, 2, 5	IA
d) Pridanie alebo nahradenie parametra v špecifikáciách v dôsledku záležitosti týkajúcej sa bezpečnosti alebo kvality		1, 2, 3, 4, 6	IB

Cieľ novelizácie nariadenia

- Zefektívnenie systému zmien
- Reakcia na technický pokrok, zvyšujúcu sa digitalizáciu, zefektívnenie postupov a odstránenie administratívnej záťaže
- Zohľadnenie získaných skúseností (napr. v oblasti biologických liekov) a riešenie nedostatkov, ktoré majú vplyv na držiteľov a regulačné orgány
- Odstránenie veterinárnych liekov

Source: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=SWD:2024:0058:FIN:EN:PDF

Timelines - Regulation

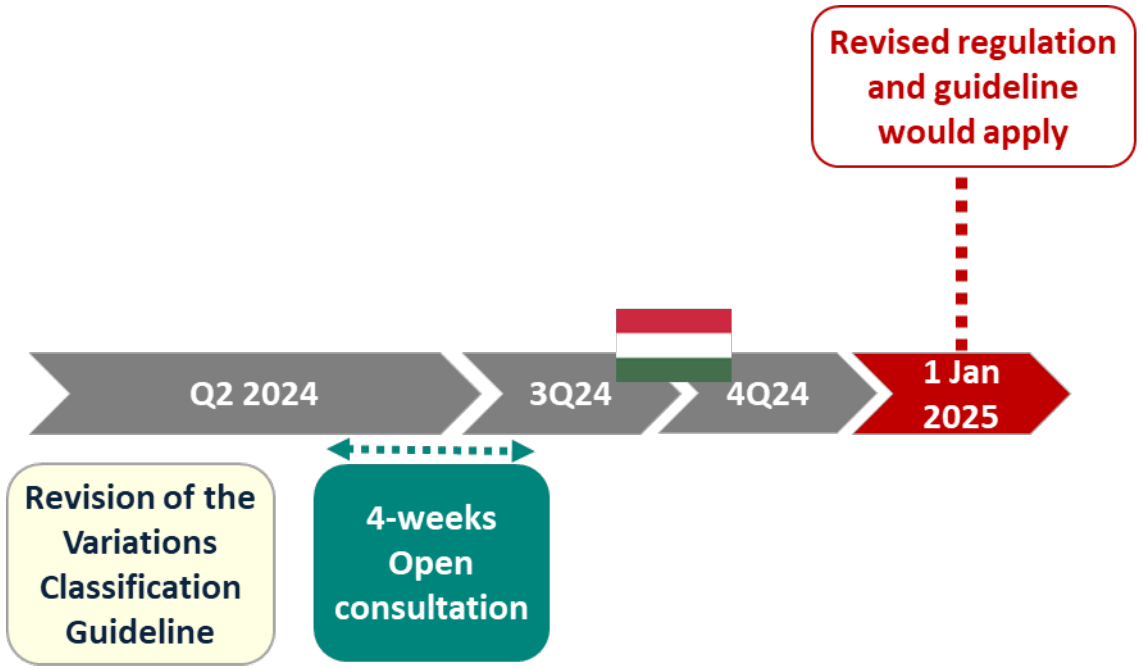


Delegated Act – faster adoption

- **Call for evidence:**
  29 Aug 2023 - 26 Sep 2023
- **Draft act:**
  07 Feb 2024 - 29 Feb 2024
- **Commission adoption:**
  11 March 2024
- **European Parliament:**
  ongoing scrutiny, awaiting ENVI decision

Sources: [Pharmaceuticals – changes to marketing authorisations (review of EU rules) (europa.eu)]
[Procedure File: 2024/2653(DEA) | Legislative Observatory | European Parliament (europa.eu)]

Timelines – Classification Guideline



- Under Assessment
- Public consultation expected between mid June till 23 Aug
- Implementation potentially delayed 3 months

Article 5 Recommendations for Unforeseen Variations

- Timeline extended from 45 (+25) to 60 days

The recommendations shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within 60 days following receipt of the request and sent to the holder, the Agency, and the coordination group.';

Type IA Variations

- Submission of Type IA variations either as annual reports or part of (super-) grouping procedures.

‘1. Where a minor variation of type IA is made, the holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV. That notification shall be submitted within 12 months following the implementation of the variation as an annual update for all minor variations of type IA or be submitted as part of grouping of variations in accordance with Article 7(2), first subparagraph, points (b) and (c), or as part of super-grouping of variations in accordance with Article 7a.

- Immediate submission of stand-alone Type IA submissions discouraged (but no change for Type IA_{IN})

By way of derogation from the first subparagraph, in justified cases, the competent authority of the reference Member State may accept the immediate submission of the notification after the implementation of the variation.’;

(Super-)Grouping of Variations

- Inclusion of super-grouping definition and extension of procedure to include purely NAPs

'Article 7a

Super-grouping of variations

1. By way of derogation from Articles 7 and 13d, the holder may submit a single notification of variations to the terms of more than one marketing authorisation referred to in Chapters II, IIa and III owned by the same holder where the same or several minor variations of type IA referred to in Article 8, Article 13a or Article 14 are notified at the same time and fall within one of the cases of super-grouping of variations listed in the guidelines referred to in Article 4(1) ('super-grouping').

2. A single notification as referred to in paragraph 1 shall be made simultaneously to the reference authority and all relevant authorities.':

Extension of CMC grouping

- … to account for related administrative changes

Annex III is amended as follows:

(a) points 6, 7 and 8 are replaced by the following:

'6. All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substances, including related administrative changes.

Worksharing

- Mandatory use of worksharing for certain procedures (“may choose to” -> “shall”).
- Shorter assessment times for Type IB worksharing variations – will follow highest variation type rather than having a standard 60-day assessment period.
- Possibility for HAs to extend the assessment period to 90 days (previously unspecified timeframe).

Worksharing

- In justified cases, may choose to follow worksharing procedure for MAs owned by several MAHs in more than one MS.

‘11. In justified cases, in accordance with the guidelines referred to in Article 4(1), when agreed by the competent authorities of the Member States and the Agency, the holder may choose to follow the worksharing procedure laid down in paragraphs 3 to 9 for the marketing authorisations referred to in Chapters II, IIa and III, where a minor variation of type IB, a major variation of type II, or a group of variations where at least one of the variations is a minor variation of type IB or a major variation of type II that does not contain any extension, relates to several marketing authorisations owned by several holders in more than one Member State.’;

Risk-Based Approach to CMC Variations

- Re-classifying some variations into lower categories and/or introducing additional flexibility, especially with regard to quality/manufacturing changes.
- Quality changes related to biological medicinal products no longer classified by default as major variations.

The following variations shall be classified as major variations of type II:

a) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

b) variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings;

c) variations related to changes outside the range of approved specifications, limits or acceptance criteria;

d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;

~~e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;~~

ICH Q12

- Allows for incorporation of some aspects of ICH Q12.

'Article 6a

Additional regulatory tools

For certain changes to the chemical, pharmaceutical and biological information for a medicinal product a holder may rely on a range of process parameters, quality attributes, protocols or summary documents, upon agreement of the relevant authority and subject to the conditions referred to in the Annexes and the guidelines referred to in Article 4(1) with regard to the specific regulatory tool.';

Seasonal & Pandemic Vaccines

- Update in multiple sections to address changes related to the replacement or addition of serotype/ strain/ antigen/ coding sequence(s) for coronavirus vaccines or other vaccines that have the potential to address a public health emergency in EU
- Immediate Commission decision

(vi) the following points (m) and (n) are added:

'(m) variations related to the replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences of a human vaccine that has the potential to address a public health emergency;

Changes related to medical devices and IVD added into Annex II Classification of variations

- Type IA

‘(g) variations related to changes to a medical device that is an integral part of or in exclusive use with the medicinal product which have no impact on the quality, safety or efficacy of the medicinal product.’;

- Type II

(n) variations related to changes to a medical device that is an integral part of or in exclusive use with the medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product.’;

Classification Guideline

- More frequent updates considering scientific/technical progress
- Agency should provide annual recommendations on unforeseen variations to be incorporated into the guidelines
- Publish electronic version of the guidelines on EC website, before the regular update

(5) Article 4 is amended as follows:

(a) in paragraph 2, the following second and third subparagraphs are added:

'The Agency, in cooperation with the competent authorities of the Member States, shall report annually to the Commission on recommendations on unforeseen variations referred to in Article 5 that result in new classification of variations and provide information on necessary updates to be included in the guidelines referred to in paragraph 1.

The Commission shall without undue delay consider the report and integrate new classification of variations and necessary updates to the guidelines.';

Classification Guideline

- In the CMD(h) competency (80% variations)
- Public consultations: mid June till 23 August

C.I.9. Zmena(-y) existujúceho systému dohľadu nad liekmi uvedené v podrobnom opise systému dohľadu nad liekmi (DDPS)	Podmienky, ktoré majú byť splnené	Dokumenty, ktoré majú byť predložené	Typ konania
a) Zmena QPPV a/alebo kontaktných údajov QPPV a/alebo záložného postupu	1	1	IA_{IN}
b) Zmena(-y) databázy o bezpečnosti a/alebo dôležitých podmienok zmlúv o plnení povinností dohľadu nad liekmi a/alebo zmena miesta, na ktorom sa vykonávajú činnosti dohľadu nad liekmi	1, 2, 3	1	IA_{IN}
c) Iná zmena(-y) DDPS, ktorá nemá vplyv na činnosť systému dohľadu nad liekmi (napr. zmena dôležitého miesta uchovávania/archivácie, administratívne zmeny)	1	1	IA
d) Zmena alebo zmeny DDPS v dôsledku vyhodnotenia toho istého DDPS v súvislosti s iným liekom toho istého držiteľa povolenia na uvedenie na trh	4	1, 2	IA_{IN}

Podmienky

1. Systém dohľadu nad liekmi zostáva nezmenený.

2. Databázový systém bol validovaný (v príslušných prípadoch).

Poznámka: C.I.9 sa vzťahuje na zmeny existujúceho systému dohľadu nad liekmi 1. pre veterinárne lieky a 2. pre humánne lieky, ktoré zatiaľ nemajú zavedený hlavný súbor systému dohľadu nad liekmi.

Poznámka pre písm. a): Keď začne fungovať databáza podľa článku 57, zmeny QPPV vrátane kontaktných údajov (telefónne a faxové čísla, poštová adresa a e-mailová adresa) možno aktualizovať jedine prostredníctvom databázy podľa článku 57 (bez potreby zmeny). Ak držiteľ povolenia na uvedenie na trh využije možnosť aktualizovať tieto informácie prostredníctvom databázy podľa článku 57, v povolení na uvedenie na trh musí uviesť, že aktualizované informácie o týchto údajoch sú uvedené v databáze.

Požiadavky priemyslu

1. Prispôsobenie sa inováciám a novým poznatkom tak, že klasifikácia zahŕňajú všetky **prvky ICH Q12 (prístup založený na riziku** uplatniteľný na všetky liečivá a lieky)
2. **Kombinácie liekov a pomôcok** a zapojenie NB
3. Zaviesť **osobitnú klasifikáciu zmien pre lieky na inovatívnu liečbu** (ATMP), ktorá zohľadňuje ich osobitosti a umožňuje neustále zlepšovanie produktov, analýz a/alebo procesov
4. Preskúmať potenciálne zavedenie klasifikácie zmien špecifických pre vakcíny a vytvoriť špecializovaný regulačný mechanizmus (“**Platform Technology Master File**”)
5. Na zníženie administratívnej záťaže a zvýšenie transparentnosti medzi regulačnými orgánmi a priemyslom (databázy/cloudové technológie) využívať **digitálne technológie**
6. Zbližovanie medzinárodnej regulácie

Ďakujem za pozornosť