Position paper

Signal detection and related safety label updates for generics in the EU.

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Problem statement

In the European Union (EU), generic medicines Marketing Authorisation Holders (MAHs) face persistent challenges in implementing safety-related product information changes (type II variations). Two interconnected problems are contributing to delays, inconsistencies, and inefficiencies in safety label harmonisation across generic medicinal products.

Problem 1:

Internal signal detection activities do not generate sufficient evidence for safety variations

Although EU regulations require **sufficient evidence** to support safety variations for both innovators and generics, in practice the operational expectations placed on generic medicine companies are misaligned with the data they can reasonably access. Generics do not hold proprietary clinical trial data, have limited access to global cumulative datasets, and rely primarily on published literature, spontaneous reports, and class-effect information. Despite this, National Competent Authorities (NCAs) frequently expect product-specific confirmatory evidence, which generic medicine MAHs are, by definition, unable to generate.

Due to this gap between regulatory expectation and realistic evidence availability generic medicines MAHs encounter Health Authority (HA) objections that their submitted evidence is insufficient *even when*:

- ➔ Mechanistic justification for the risk is strong,
- ➔ Literature and retrospective studies support the association, and
- ➔ Regulatory precedent for class effects exists.

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Examples:

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) and oligohydramnios (2020–2022)
Considering mechanistic understanding and published case analyses showing the risk of oligohydramnios from NSAID use at ≥20 weeks gestation, several generic medicines MAHs attempted to proactively submit safety variations reflecting this risk. However, many NCAs rejected these Type II variation applications on the grounds of "insufficient evidence," primarily because the reference product label had not yet been updated and no PRAC-driven guidance was underway.
This resulted in nearly two years of fragmented national decisions, with some NCAs requesting wording updates, others rejecting submissions, and several instructing generics to await an originator or PRAC signal review. Only after PRAC and CMDh initiated a coordinated, class-level review was a harmonised text agreed and implemented across all MAHs to ensure consistent safety messages to patients and caregivers.

Beta-lactam antibiotics and SCAR (2019–ongoing)
Some national competent authorities (NCAs) triggered label updates to include Severe Cutaneous Adverse Reactions (SCAR) for all beta-lactam antibiotics. However, internal signal detection activities within generic medicine companies rarely yield product-specific evidence strong enough to justify type II variations, and certainly not at the product class level—despite extensive literature indicating cross-reactivity and class association. This limits generic medicine companies' ability to proactively initiate aligned safety label updates.

Problem 2:

Variations submitted by one MAH result in inconsistent labels and follow-up variation requirements for other MAHs

When a single MAH submits a safety variation (often after receiving HA request), the outcome frequently creates **inconsistency across generic medicine labels** because:

- ➔ Other MAHs may not have the same level of evidence to support the variation, even when a safety concern is applicable to the identical active substance.
- ➔ Not all NCAs consistently apply the same expectations.
- ➔ Reference product labels may not yet reflect the change.
- ➔ Instructions for variation type (IB vs. II) may differ across products and Member States.

- ➔ Multiple waves of follow-up variations imposed on other MAHs after the first variation is approved.
- ➔ Duplicative assessment workload for NCAs and CMDh.

Result:

Safety information for products within the same class—or even the same active substance—becomes fragmented across the EU, with some products' safety information updated and others not. This situation exposes generic medicines MAHs to avoidable regulatory requirements and results in unequal safety information being provided to patients. Furthermore, NCAs are conducting parallel evaluations of the same safety concern across submissions from multiple MAHs, resulting in unnecessary duplication of assessment activities and avoidable regulatory burden as well as unnecessary fees for MAHs. These parallel assessments are often repeated independently by NCAs in other Member States, further amplifying the inefficiency. Often these fragmented implementation challenges have a downstream effect to supply chains, impacting accessibility of essential medicines to patients.

Proposal

The following approaches are, therefore, proposed **for generic medicines**, to rationalise and harmonise signal detection and safety label updates across MAHs, with the objectives to

1. consider the complete dataset across all MAHs for signal detection and evaluation
2. take actions across all MAHs consistently (at the same time and with the same actions)

1. Establish a single EU/EEA common product label maintained centrally, ensuring synchronised safety updates for all MAHs

We suggest that the EMA mandate a single EU/EEA common product label to serve as the harmonised reference for all generic medicinal products. This common label should be maintained by the common label's MAH, and any approved safety label changes should be published on the EMA's official webpages, ensuring transparent and simultaneous access for all MAHs.
Where an originator product is no longer authorised or available in the EU/EEA for generic medicines, the common label should be designated from an authorised medicine, based on predefined and transparent criteria such as market share, breadth of EU/EEA product approvals, etc.
Implementing this approach would deliver clear efficiencies for the Agency by significantly reducing the volume of partially overlapping and duplicative data submitted by multiple MAHs, thereby decreasing the assessment burden and shortening review times for variation submissions. A single

centrally maintained common label would also enhance consistency of product information across Member States, improve harmonisation in the interest of patient safety and product interchangeability, helping to address drug shortages, and simplify the ongoing maintenance of product labels across the EU/EEA for both regulators and MAHs.

2. Implement a structured signal-notification pathway allowing generic medicines MAHs to communicate validated safety signals to EMA/PRAC

We suggest that the EMA establish a signal notification pathway for generic medicinal products, enabling generic medicines MAHs to notify the EMA/PRAC of validated safety signals in situations where individual MAHs do not hold sufficient standalone evidence to support a safety variation. Notification submissions should include a concise summary, source(s), preliminary assessment, urgency level, proposed scope (product or class), and suggested next steps (e.g. inclusion in the next PSUR/PSUSA or ad-hoc PRAC review). The EMA/PRAC should triage the notifications, inform the submitting MAH of the triage outcome and subsequent actions, request cross-MAH data aggregation where appropriate, and communicate the outcome and any required variations, to all MAHs simultaneously. This centralised approach would prevent fragmented national outcomes, reduce duplicative efforts across MAHs, and facilitate timely EU-wide harmonisation of product information.

References

1. Report from the CMDh meeting held on 19-20 July 2022: NSAID-containing medicinal products (for systemic use) and use during pregnancy. 29 July 2022.
2. Report from the CMDh meeting held on 13-14 September 2022. NSAID-containing medicinal products (for systemic use) and use during pregnancy. 22 September 2022.