Proposals and further steps regarding off-label use in the European Union

HMA Subgroup on Timely Access

Whereas the EU legislation does not regulate the practical use of medicinal products, regarding prescription or their use extending over the terms of marketing authorisations (on and off-label use), there are many regulations at member state level. The specific aspects of off-label use can be laid down in law or in clinical practice guidelines issued by international or national professional bodies. In other words, therapeutic principles are provided simply by these guidelines or some obligations on healthcare professional can be imposed by a decree. The national competent authorities can also substantiate any guidance or policy.

Nowadays the collection of relevant information in connection with off-label use is very demanding and even difficult for several reasons. The sources of information can be found randomly, to discover them is time-consuming and the linguistic challenges request significant human and financial resources as well.

Proposals

The aim of this initiative is to create a common understanding of the issues. The aim is not to create harmonised regulation across borders.

Taking into account these premises, the proposal of this subgroup to the HMA is directed towards a triple objective: a) to propose a well-defined scope of collaboration between the Member States; b) to set up an informal network of national points of contact to exchange information regarding this issue; and c) to foster collection of data.

a. Scope of collaboration

There is no legal definition of off-label use in the EU pharmaceutical legislation. According to the widely accepted definition, off-label use includes any use of the authorised medicinal product outside the terms of its marketing authorisation in the general clinical practice. Furthermore the Guideline on Good pharmacovigilance practices (GVP) - Annex I - Definitions (Rev 4) - defines off-label use as “Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.” Examples include a different indication in terms of medical condition, a different group of patients (e.g. a different age group), a different route or method of administration or a different posology (either increasing or decreasing the dose). The reference terms for off-label use are the terms of the marketing authorisation in the country where the product is used.

From a practical point of view, several examples of off-label use may be considered as all of them may have different potential implications. Whereas co-operation at member states level might be tightened in various fields, for the purpose of this reflection paper the focus of collaboration could be on the following areas, as they may benefit from both exchange of information and a harmonised approach:

- Off-label use of recently approved (on-patent) medicines. This sometimes occurs in indications for which the MAH has a clinical programme ongoing (this situation may be seen as very close to compassionate use programmes) while other times does not. In both cases, there is an impact on payers that usually complain of paying for a medicine before it is approved and a decision on P&R is made.
- Off-label use of old, off-patent medicines. There are multiple examples. Repurposing might be the potential solution for this subset (refer to the repurposing pathway discussion at STAMP).
The other areas of off-label use, such economic off-label and off-label not related to indications but other parts of the SmPC (e.g. target population, dosage or pharmaceutical forms), would not be within the scope of this collaboration between Member States.

In some cases these off-label uses fall under some of the above described categories (e.g., reducing the dosage of a given medicine on increasing the administration interval for economic reasons) but other times reflect only changes in the way medicines are used (e.g., administration in the pediatric population while no data exists in the dossier).

b. Network of national points of contact (PoC)

To establish a network of contact points at the NCA level who are well informed in legislative and practical issues, regarding usage of medicinal products in the concerned member state seems to be reasonable and could add a significant value. These contact persons can work within the frame of the HMA network. Similar networks (e.g. Network Innovation) are already in place in the EU e.g. European reference network.

The network of points of contact on off-label use can facilitate the exchange of information (therapeutic guidelines including off-label use, specific legislative tools, etc), and can foster a harmonised approach but may also highlight to the regulators a good or beneficial clinical practice.

The PoC may communicate by e-mail and join in virtual meetings to establish any further collaboration. If needed, this network of PoC may also collaborate in expanding the work done by STAMP regarding repurposing at national level.

c. Collection of data

One of the objectives of the network of PoC would be to serve as a cataliser to foster the collection of essential data on a specific off-label use across MSs but also to promote a harmonised approach on further data gathering in order to facilitate the transformation of an off-label use to on-label when appropriate. This may occur, for example, by promoting common registries to obtain real world data or helping academia in performing low interventional trials.

It would be important to liaise with other groups to avoid duplication of efforts is also important (e.g., the CTFG to promote an harmonized view on low-interventional clinical trials or studies, the big data TF to consider use of different data souces for the purposes of off-label use, and/or the EU-IN for guiding academia in developing studies and collection of existing data on off-label use).

Proposed road map

- Presentation of proposal of the subgroup to Heads of Medicines Agencies
- Adoption of proposals on off-label use by Heads of Medicines Agencies
- Appointment of national contact points
- Establishment of the network and drawing its rules of procedures up
- Compilation the working plan of the network
- Mapping the links between other networks / working groups