The European Association of Medical devices Notified Bodies

Team-NB Position Paper

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Data generated from 'Off-Label' Use of a device under the EU Medical Device Regulation 2017/745.

'Off label use' is mentioned within the Medical Device Regulation (MDR) in Annex XIV Part B, in the context that manufacturers should proactively identify misuse or off-label use of their device through PMCF activities, however 'off label use' or 'misuse' is not defined within the MDR.

Searching the term 'off-label use definition' will provide many definitions in relation to pharmaceuticals but yield limited results for a definition associated specifically with medical devices. However the interpretation of off label can be considered generally the same.

Table 1 provides some common interpretations from various regulators and medical device organizations of the term 'off-label' in the context of medical devices

Organization	**Definition/Interpretation**
Medicines & Healthcare products Regulatory Agency (MHRA), the UK regulating authority1[1]	You should use medical devices as described by the manufacturer in the instructions. If you use the device in any other way, it's considered 'off-label' use
Therapeutic Goods Administration – The Australian Regulating Authority[2]	'Off-label use' generally refers to the use of a therapeutic good for an indication or intended purpose that is not specified in its Australian Register of Therapeutic Goods (ARTG) entry. Therapeutic goods are included in the ARTG with either specific indication(s) or intended purpose(s).
Medical Device Network[3]	Any information that comes with a product is considered labelling and when the product is used for a clinical indication that is not approved, it is regarded as off-label use.

Table 1 – Definitions/Interpretations of Off-Label Use for Medical Devices

Off-label use of a medical device is generally accepted to mean when a device is used outside of the approved instructions for use including indications.

[1] https://www.gov.uk/government/publications/medical-devices-off-label-use/off-label-use-of-a-medical-device
[2] https://www.tga.gov.au/label-use-medical-devices-frequently-asked-questions
[3] https://www.medicaldevice-network.com/comment/commentoff-label-use-of-medical-devices-5820363/

Specifically off-label use of a device outside the approved indications could include the use of a device*;

- Outside specified populations such as paediatrics;
- For a different stage or severity of disease
- For a similar (not identical) clinical condition
- Being introduced to the body through alternative routes

**Note: This is an example list and not an exhaustive list.*

Under Article 7 clause (d)[4] of the MDR, manufacturers must not promote the misuse of a device and manufacturers should as part of the general safety and performance requirements (GSPR) consider the potential foreseeable misuse of the device[5]. When misuse is identified the manufacturer shall eliminate or control the risks[6] in accordance with risk control measures.

Foreseeable misuse may be identified through usability studies or pre-market clinical investigation reports, but it is often difficult for manufacturers to predict areas of future misuse and without the manufacturer having direct supervision over the use of each individual device, it is inevitable that in off-label use may occur.

Physicians and healthcare practitioners who use a medical device off-label are accountable for their actions and such use of a device could result in local law enforcement procedures or potential implications to their national/state registration. The use of a device within its intended purpose and indications fundamentally supports the principles evidence-based medicine.

However, there are occasions when physicians and healthcare practitioners through the experience and use of a device under approved conditions, identify potential solutions to other problems that could benefit a subset of patients that are outside the on-label use of the device.

For example in the context of a situation where there is an unmet medical need, and no other approved viable alternatives are available it could be ethically acceptable for a physician to consider alternative options. Such use of a device is often reported as individual case studies within peer reviewed literature and manufacturers may identify such off-label use as part of their general post market activities through literature searches. This identified data should always be considered as part of the clinical evaluation of a device in addition to the already mentioned GSPR of Annex I of the MDR to reduce or eliminate the risks of future misuse.

[4] EU MDR 2017/745 Article 7 – *(d) suggesting uses for the device other than those stated to form part of the intended purpose for which the conformity assessment was carried out.*

[5] EU MDR 2017/745 Annex I Clause 3 *(c) - estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;*

[6] EU MDR 2017/745 Annex I Clause 3 *(d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4;*

The MDR requires that the manufacturer's post market clinical follow up (PMCF) plan must identify *systematic misuse or off-label use of the device with a view to verifying that the intended purpose of the device is correct*.[7]

In this context, 'systematic' should be interpreted when a device is used repeatedly or continuously outside its approved intended purpose and indications. This should be considered different to the earlier example of the unmet medical need where a device has been used 'unsystematically' meaning randomly.

The identification and results of systematic misuse of the device should be reported within the PMCF evaluation report and consideration of its overall impact in the context of risk management should be applied.

When systematic off-label use has been identified through the PMCF plan and reported upon, this may be considered as clinical data. The MDR does require that both favourable and unfavourable data is considered as part of the clinical evaluation.[8]

This understanding of 'off-label' data being considered clinical data is further clarified through the interpretation of 'clinical data' under article 2 and definition 48 of the MDR and mentions specifically the use of data coming from post market clinical follow up.

> **'Clinical data'** means information concerning safety or performance that is generated from the use of a device and is sourced from the following:
>
> — clinical investigation(s) of the device concerned,
>
> — clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,
>
> — reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
>
> — clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up;
>
> (Article 2 (48) EU MDR 2017/745)

[7] EU MDR 2017/745 Annex XIV Part B Clause 6.1 *(e) identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct.*

[8] EU MDR 2017/745 Annex XIV Part A Clause 2 *The clinical evaluation shall be thorough and objective and take into account both favourable and unfavourable data.*

As part of the clinical evaluation the manufacturer should consider the off-label data as part of the overall clinical evaluation, as reported per the requirement in Annex XIV to plan, continuously conduct and document a clinical evaluation.[9]

Can off-label data be used to expand the intended purpose/indications?

The manufacturer is required per Article 61 of the MDR to specify and justify the level of evidence to demonstrate conformity with the general safety and performance requirements of the MDR taking into consideration the intended purpose of the device.[10] As part of this assessment the 'sufficiency' of this data needs to be considered. Sufficiency should be interpreted within this context to mean both quality and quantity.

Off-label data typically does not have 'sufficiency'. Whilst it may hold sufficient quantity, particularly if systematic off-label use has been identified, it however will often fail to have sufficient quality in terms or meaningful conclusions.

Off-label data is typically collected outside any formal protocols and the absence of any protocols ultimately results in the lack of sufficient quality and the inability to be able to draw evidence-based conclusions.

When considering the hierarchy of clinical evidence it would be typically assumed that data generated from off-label use outside of a controlled protocol would be low and could be considered to hold similar weighting to clinical evidence for individual case studies.

When manufacturers identify systematic off-label use they should take appropriate measures not only to reduce the misuse but also to consider whether there is a genuine need within the medical community for the newly identified use in relation to the specific medical purpose/indication.

If the conclusion of this consideration is favourable, then manufacturers should proceed to formalise the process of collecting the data and follow the requirements of the MDR. This may include the need to set up a clinical investigation to focus on this identified use. The MDR is clear that any clinical investigations that are conducted outside of the scope of the intended purpose of a CE marked device must follow the same requirements of a pre-market clinical investigation.[11]

Collecting data outside of the intended purpose in a formal manner such as a controlled clinical investigation with a robust protocol and appropriate statistical analysis plan is likely to yield sufficient quality and quantity data that can be leveraged to support a conformity assessment.

[9] EU MDR 2107/745 Annex XIV Part A Clause 1 *To plan, continuously conduct and document a clinical evaluation, manufacturers shall..*

[10] EU MDR 2017/745 Article 61 Clause 1 - *The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.*

[11] EU MDR 2017/745 Article 74 Clause 2 - *Where a clinical investigation is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 20(1), Articles 62 to 81 shall apply.*

Derogation from Conformity Assessment Procedures for a Medical Device for an Unmet Medical Need

There are circumstances that a device may be used for an unmet medical need for example for the diagnosis or treatment of a rare disease condition for which the device has not been approved. There are in such circumstances limitations in the collection of sufficient data, where often both sufficient quality and quantity cannot be achieved for a meaningful conclusion.

In such circumstances, it may be possible for manufacturers to consider requesting derogation from conformity assessment procedures for the use of the medical device under Article 59 of the MDR. This request should be made to the competent authority of the member state for which the device is intended to be used. [12]

[12] EU MDR 2017/745 Article 59 Clause 1 - *By way of derogation from Article 52, any competent authority may authorise, on a duly justified request, the placing on the market or putting into service within the territory of the Member State concerned, of a specific device for which the procedures referred to in that Article have not been carried out but use of which is in the interest of public health or patient safety or health.*