

WHITE PAPER:

Off-label use of medical devices

DISCLAIMER

TOOsonix A/S makes no warranties with respect to the information set forth in this document or the products to which the information refers.

Accordingly, TOOsonix A/S will not be responsible for damages resulting from use of or reliance upon this information.

Revision:	1
Created by:	Torsten Bove
Review by:	Tomasz Zawada
Approved by:	Torsten Bove
Date of version:	October 5 th 2021
Signature:	

Introduction

Any medical device comes with a specific intended purpose, giving information on its users, patient population, indications, use environment, working principles, contraindications, precautions and potential side-effects. This has been filed and/or approved by a national/regional authority (e.g. by CE-marking or FDA clearance). The information, combined with all other written information provided with the device, is called *labelling*.

Medical legislation generally prohibits manufacturers of medical devices to suggest uses for the device other than those stated in the product labelling (see for example MDR EU 2017/745 Art.7)

When physicians use devices for treatment that are not directly described in the labelling anyway, it is generally referred to as *off-label use*. These treatments are therefore not covered by the medical authorities' normal processes for treatment or post-marketing activities.

The medical legislation and authorities however only regulates and governs the approval of medical products, but not the *practice of medicine*. It is always the physician that is the primary responsible for determining the appropriate treatment in an individual situation. Good medical practice and the best interests of the patient can therefore often require physicians to select an off-label treatment as standard-of-care or case-based treatment in certain situations. Use of a marketed product in an off-label manner, when the intent is the *practice of medicine*, therefore does not always require formal approval from authorities.

Requirements for off-label use

While general guidelines on off-label use of medicinal products have been published for most jurisdictions, there is unfortunately very little formal help or guidelines specifically relating to off-label use of medical devices. Based on case-law (mostly from USA) and general guidelines from publicly available sources and well-described medical practice, the following accepted obligations for off-label use can however be composed:

- If a physician use a medical device in an off-label treatment, he/she has the responsibility to be well informed about the product, to base its use on firm scientific rationale and sound medical evidence, and to maintain records of the product's use and effects.
- The physician will be responsible for the off-label use and the consequences thereof.
- The physician using a medical device in off-label treatment should always consider and be able to rationalize the risks and potential impact on the safety and performance.
- Prior to treatment, the physician must always inform the patient of the investigational nature and make a note in their records that they will be using the medical device off-label. This documentation should form a part of the consent procedure.
- Specific local and/or national policies regarding off-label use, e.g. consent procedures etc., may need to be observed.

Off-label use in the daily practice

Despite the above-mentioned regulatory implications and increased responsibilities imposed on the physician, off-label use is widely performed in hospitals and private clinics as a necessary part of their daily *practice of medicine*. Typical examples of treatments performed on labelled indications, but in an off-label mode include:

- Treatments on pregnant, lactating, transplanted, chronically ill, psychiatric or pediatric patients etc. Clinical investigations (at least in the earlier phases of a product life-cycle) often do not include populations outside healthy adults. All treatments on patients outside this group is consequently considered off-label use.
- The standard-of-care treatment has failed and no other standard alternatives that promises different results are available. In such cases the physician's may choose off-label use, e.g. by adjusted treatment settings or changed treatment frequency.
- Ambiguously diagnosed conditions. Many conditions can often fall under several different partial diagnoses, some of which are included in the device labelling, while others are not. This is particularly the case with benign or low-risk conditions, that might not be eligible for full detailed diagnosis before treatment.
- Medical versus aesthetic use is a gray area. The performance of aesthetic procedures cannot be directly documented by clinical investigations, as the regulatory requirements for these are to demonstrate a sufficient safety profile only (aesthetic treatments can per definition not demonstrate a curative effect). Treatments of benign medical conditions outside the device label, performed on the basis of an labelled aesthetic consideration, may therefore debatable fall under off-label use.

Off-label use for exploratory therapy

In addition to the frequent use of devices outside its clearly defined population, settings and list of specific indications, off-label use is furthermore highly relevant in a range of experimental and exploratory treatments using new devices or methodologies.

Examples of situations where off-label exploratory devices or methods can be justified based on the argument for a physicians *practice of medicine* are:

- Other treatment methods have failed and no other standard alternatives that promises different results are available.
- Patients are actively requesting alternative methods due to personal preferences, such as considerations to pain, efficacy, down-time, risks of complications during healing, or adversity towards ionizing radiation or specific pharmaceutical products.
- Individual patients are volunteering for case-based experimental treatments after careful and informed assessment by a trained physician, concluding that the risk of the new treatment is comparable, or lower, than the standard-of-care treatment.
- Individual patients having very similar conditions to a labelled indication as assessed by a trained physician, and a conclusion that the risk of the new treatment is comparable to the existing approved treatments by the device.

Exploratory therapy can be particularly useful in the very early phases of clinical testing, where feasibility and clinical settings of a device used on new indications are not fully established. Exploratory treatments can then be used to establish the treatment settings that are later formalized in the protocol of a larger clinical investigation.

Investigational use

It is important to distinguish the above *practice of medicine* and exploratory therapy from *investigational use*. Both types fall under off-label use, but *investigational use* refers to larger

populations selected systematically from pre-determined inclusion- and exclusion criteria. Investigational use has to be formalized and follow the process for GCP clinical investigations (defined in ISO14155: 2020), and must be approved by relevant ethics and medical authorities before patients are recruited and treatments are started.

Conclusions

Off-label use of medical devices involves using therapies for an indication, device-setting, or population that has not been approved by relevant medical authorities.

Since the medical authorities do not regulate the *practice of medicine*, off-label use has always been common, and a necessity to serve the best interest of patients. It occurs in every specialty of medicine, and is in particular very common in areas where the patient population is less likely to be included in clinical investigations (e.g. pediatric, pregnant, or psychiatric patients).

To limit personal liability, physicians should prescribe off-label therapy only for indications that they believe are in the best interest of the patient on the basis of the available evidence. Physicians should therefore always carefully consider the risks and potential impact on the safety and performance of the treatment before it is started. In cases where off-label use is justified, it can however promote both patient satisfaction and medical progress significantly.

It is often through exploratory off-label use that new medical innovation is made, and physicians should therefore continually educate themselves about off-label use to weigh the risks and benefits and provide the best possible care for their patients.

Links to guidelines on off-label use:

TOOsonix System ONE-M Indications for use:

<https://www.toosonix.com/instruction-for-use/>

European Commission report on off-label use of medical products – Executive Summary

https://ec.europa.eu/health/sites/default/files/files/committee/stamp/stamp6_off_label_use_background.pdf

European Commission report on off-label use of medical products – Full report

https://ec.europa.eu/health/sites/default/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

FDA Info-sheet:

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices>

UK Guidelines on off-label use:

<https://www.gov.uk/government/publications/medical-devices-off-label-use/off-label-use-of-a-medical-device>

Ten Common Questions (and Their Answers) About Off-label Drug Use

[https://www.mayoclinicproceedings.org/article/S0025-6196\(12\)00683-0/fulltext](https://www.mayoclinicproceedings.org/article/S0025-6196(12)00683-0/fulltext)

Examples of publications on off-label use in dermatology (open access)

- Stuart D. Shanler, Andrew L. Ondo. Successful Treatment of the Erythema and Flushing of Rosacea Using a Topically Applied Selective alpha1-Adrenergic Receptor Agonist, Oxymetazoline. Arch Dermatol. 2007;143(11):1369-1371.
- Wollina U. Erbium-YAG laser therapy – analysis of more than 1,200 treatments. Glob Dermatol, 2016, Vol 3(2): 268-272
- Steven Nisticò, Piero Campolmi, Silvia Moretti et al. Nonconventional Use of Flash-Lamp Pulsed-Dye Laser in Dermatology. BioMed Research International; 2016: 1-6.
- Theodore Rosen, Kami Lowery. Superficial Basal Cell Carcinoma of the Face Successfully Treated with Ingenol Mebutate 0.05% Gel: Case Report and a Review of the Literature. J Clin Aesthet Dermatol. 2020 Oct;13(10):28-31
- Emily Wenande; Niels Bech-Thomsen; Katrine Togsverd-Bo et al. Off-Label 9-Valent Human Papillomavirus Vaccination for Actinic Keratosis: A Case Series. Case Rep Dermatol 2021;13:457–463.
- Giuseppe Monfrecola, Matteo Megna, Chiara Rovati et al. A Critical Reappraisal of Off-Label Use of Photodynamic Therapy for the Treatment of Non-Neoplastic Skin Conditions. Dermatology 2021;237:262–276.
- Nita Wienholtz, Messoud Ashina, Jacob, P. Thyssen, Alexander Egeberg. Subtype-Specific Off-Label Treatment of Rosacea. Case Rep Dermatol 2021;13:121–128.
- Piyu Parth Naik. Utilities of Botulinum Toxins in Dermatology and Cosmetology. Clinical, Cosmetic and Investigational Dermatology 2021;14 1319–1330.
- Martina Ghezzi, Silvia Pescina, Andrea Delledonne, Ilaria Ferraboschi, Cristina Sissa et al. Improvement of Imiquimod Solubilization and Skin Retention via TPGS Micelles: Exploiting the Co-Solubilizing Effect of Oleic Acid. Pharmaceutics 2021, 13, 1476, 1-23.
- Klara Cvenkel, Mateja Starbek Zorko. Challenges in the treatment of psoriasis in childhood. Acta Dermatovenerol Alp Pannonica Adriat. 2021 Sep;30(3):105-108.