OFF-LABEL USE IN OPHTHALMOLOGY

Know the important considerations for the use of surgical techniques, medical devices, and drugs beyond their approved purposes.

BY MICHAEL ZACH

Whether and to what extent a surgical technique, medical device, or drug is used depends on a variety of factors that include legislative guidelines, the manufacturer's application for approval, and reimbursement rules. Within this regulatory framework, a physician's decision on use have legal consequences that extend far beyond the OR.

OFF-LABEL USE IS NOTHING NEW

Extending the use of a medical device, drug, or even procedure beyond its approved indication[1] or purpose is a practice as old as the medical device approval process itself. Before we delve into specific areas in ophthalmology, one general guideline is that the decision to use something off-label should be based on the physician's level of expertise.

In other words, as so-called learned intermediaries, physicians determine whether to deviate from a manufacturer's approved instructions on a case-by-case basis. Off-label use has become so common, in fact, that refusing it may be regarded as a medical error.

EXAMPLES

Let's review some examples of common off-label–use procedures in ophthalmology.

Refractive lens exchange. IOLs intended by the manufacturer to be placed at the time of cataract surgery to replace the cataractous lens are often also used for refractive lens exchange (RLE). Many surgeons support this practice because the surgical procedures are basically the same. There are, however, some considerations.

First, the off-label use of an IOL for RLE is supportable if it can also produce a positive effect for the specific patient (eg, IOP reduction), and an equally suitable IOL is not available for on-label use.

Second, the clearer the surgical indication for RLE, the stronger is the case for the off-label use of an IOL in this setting. It is worth mentioning that, according to international consensus, a clear medical indication for refractive surgery exists only with the diagnosis of high myopia (ie, -6.00 D or more). Also worth mentioning is that private insurers must reimburse well below this value,[2] particularly for RLE.[3]

When RLE is an appropriate treatment option for patients, the next consideration is whether the off-label use of the chosen IOL is appropriate (see *Assessing a Medical Standard*). Factors such as an increased risk of retinal detachment in myopic patients under the age of 50 are relevant to the preoperative discussion of RLE but are not contraindications to the off-label use of the IOL.

Third, in addition to discussing the risks, benefits, and cost of RLE with patients before surgery, surgeons must also disclose that the chosen IOL will be used in an off-label fashion.

Piggyback IOLs. The placement of a piggyback IOL is one approach to managing residual refractive error after cataract surgery. Again, certain considerations must be weighed before deciding to use the lens in an off-label fashion. First, the use of a phakic IOL in a pseudophakic eye is off-label. Second, even if the indication for piggyback IOL implantation is established, other surgical alternatives such as PRK and LASIK must also be considered. It is up to the physician to decide whether an off-label use of a piggyback IOL is supported by the initial findings in an individual case (see *Assessing a Medical Standard*). Just as with RLE, surgeons must discuss not only the risks and benefits of piggyback IOL implantation with patients but also that the procedure involves the use of a device beyond its approved purpose.

Primary posterior laser capsulotomy. A femtosecond laser is often used beyond its primary approved area of application, such as immediately after cataract surgery in primary posterior laser capsulotomy to decrease the occurrence of posterior capsular opacification. This procedure is not purely prophylactic in nature because the risk of posterior capsular opacification is caused by cataract surgery. Antibiotic prophylaxis has the same objective.

Phacoemulsification versus laser cataract surgery. It is worth noting that a standard procedure can lose its medical indication. For example, laser cataract surgery may be preferable to phacoemulsification for an eye with a greatly reduced endothelial cell count. One can argue against performing phacoemulsification in this situation even though the manufacturer's instructions do not describe a limitation in the scope of application of ultrasound. In this respect, the manufacturer's instructions do not provide exoneration for the physician if laser treatment has emerged into medical standard and is preferable in the case of reduced endothelial cell count.

DEVICE VIOLATIONS

The cases of off-label use described earlier in this article are all therapeutically motivated and may thus be justified for a particular patient. Off-label use

ASSESSING A MEDICAL STANDARD

The decision to extend the use of a surgical technique, medical device, or drug beyond its approved indication requires the physician to consider whether a medical standard for the intended off-label use has been established. The following factors can be considered when making this assessment.

- The position of public bodies or civil courts regarding reimbursement in the case of this off-label-use
- How widespread the off-label use is
- Current discussion in scientific discourse
- Inquiries submitted to the manufacturer regarding postmarket surveillance
- The absence of an on-label alternative

that is otherwise motivated, such as the repeated use of a medical device designated for one-time use by the manufacturer, is punishable by law. That is also true of combining a coagulation laser device for the treatment of retinal detachment with the endolaser probes from another manufacturer contrary to the manufacturer's instructions and without corresponding proof of conformity. This is a clear violation of legal regulations designed to ensure that medical devices are used only in accordance with their intended purposes. Such off-label uses are neither foreseeable nor avoidable by the manufacturer. Provided that the user instructions are sufficiently clear, the consequences of any deviation from the manufacturer's instructions in these cases are the sole responsibility of the physician who uses the device.

Regulations are also clear when it comes to the misuse or abnormal use[4] of a medical device. In the case of deliberate misuse, the user cannot expect the product to be safe and not to pose any danger. The manufacturer is not liable but is obliged to observe the market. The intended purpose of a medical device is subject to the power of the manufacturer's definition, which states the manufacturer's approved indications.

A manufacturer is expected to have an economic interest in the broadest possible field of indications and the narrowest possible field of contraindications. Nevertheless, contraindications can be found in the instructions for various products. The operating instructions of a femtosecond laser, for example, include contraindications for corneal anomalies of all kinds and for pediatric applications. Pediatric applications are typically used at the discretion of the physician beyond the scope of the marketing authorization. Likewise, absolute contraindications listed in the instructions for one IOL are "macular degeneration [and] irregular corneal astigmatism with unstable refraction."

A comprehensive list of contraindications promotes the manufacturer's economic interest in avoiding liability for material defects if a physician uses the medical product in a contraindicated manner. The manufacturer is also spared the effort and expense of market surveillance when a device is used abnormally in practice. For example, a patient whose IOL becomes cloudy may have a legal claim against the manufacturer—because liability exists regardless of culpability—unless the IOL was used in a manner specified as contraindicated by the manufacturer. Therefore, in cases such as this, when the physician has essentially deprived the patient of a potential liability claim against the manufacturer, the physician has a duty to inform the patient about the (potential) economic effect of contraindicated use and to discuss alternative on-label products.

Contraindicated uses of medical devices should of course be avoided, and on-label products should be used when available.

PHARMACEUTICAL VIOLATIONS

According to product labeling, bevacizumab (Avastin, Roche) is not indicated for treatment of age-related macular degeneration (AMD). However, ranibizumab (Lucentis, Novartis), a drug based on the same compound from Genentech and approximately 30 times more expensive, is indicated for the treatment of AMD. Interestingly, Novartis owns shares in Roche, a company that acquired a majority stake in Genentech in 2009. Novartis and Roche shared in the revenues of that compound, both when used on-label (ranibizumab) and off-label (bevacizumab). This gives the impression of an abusive delineation of indications because both drugs appear to be equally effective for the treatment of AMD.

Italy's national health insurance system paid for the off-label use of bevacizumab for AMD (ie, use outside the EU marketing authorization)—rightly so, as the European Court of Justice (ECJ) ruled.[5] The ECJ states that the European Union does not prohibit prescribing a medication outside its traffic permission. In so ruling, the ECJ also supported physicians' off-label use of the drug, to which Novartis had objected.

CONCLUSION

It is not advisable for physicians to adhere blindly to a manufacturer's instructions. Instead, the focus of medical treatment should always be on the individual patient. Deviation from a manufacturer's instructions may be permissible or even necessary in an individual case or for an entire group of cases.

If contraindications are listed in a manufacturer's instructions, physicians may question their basis and whether they are, in fact, merely untested areas of application. Patients must always be informed of any deviation from a manufacturer's instructions, and whenever possible, medical devices, drugs, and techniques should be used for their approved purposes. ■

1. European Commission Medical Devices Regulation, Article 2, No. 12.
2. Federal Supreme Court (BGH), Ruling 29.03.2017, IV ZR 533/15.
3. Stuttgart Higher Regional Court (OLG), Urt. v. 28.03.2019, 7 U 146/18.
4. European Commission Medical Device, MEDDEV 2.12-1: Guidelines on a Medical Vigilance System, Ziff. 4.1.
5. European Court of Justice (ECJ), Urt. v. 21.11.2018, C-29/17) on a proposal from the Italian Council of State (consiglio di stato).

MICHAEL ZACH
■ Medical Law Attorney, Mönchengladbach, Germany
■ info@rechtsanwalt-zach.de
■ Financial disclosure: None