Biomarkers and Surrogate Endpoints in Drug Development: A European Regulatory View

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PURPOSE. To give a European regulatory overview of the requirements on and the use of biomarkers or surrogate endpoints in the development of drugs for ocular disease.

METHODS. Definitions, methods to validate new markers, and circumstances where surrogate endpoints can be appropriate are summarized.

RESULTS. The key endpoints that have been used in registration studies so far are based on visual acuity, signs, and symptoms, or on surrogate endpoints. In some ocular conditions, established outcome measures such as those based on visual acuity or visual field are not feasible (as with slowly progressing diseases), or lack relevance (e.g., when central visual acuity may be preserved even though the patient is legally blind owing to a severely restricted visual field, or vice versa).

CONCLUSIONS. There are several ocular conditions for which there is an unmet medical need. In some of these conditions, surrogate endpoints as well as new clinical endpoints are needed to help speed up patient access to new medicines. Interaction with European regulators through the pathway specific for the development of biomarkers or novel methods is encouraged.

Keywords: regulatory, clinical research, biomarker, validation, drug development

Whilst regulators are open to engaging on a broad range of novel approaches, in this article we focus on biomarkers. We define these as measures of clinical, pathologic, or physiological processes. These can be imaging, bioanalytic, or other methods. Some biomarkers could evolve to act as surrogate endpoints where appropriate (see below) and may be used in therapeutic trials, substituting for the clinical endpoint. A clinical endpoint is one that is of a direct importance for the patient with an ocular disease, that is, one that evaluates how the patient functions or feels (see European Medicines Agency [EMA]: EU Regulatory Workshop - Ophthalmology³ and should reflect the accepted norms and standards in the relevant field of research. Clinical relevance of primary and secondary efficacy endpoints must be justified. Such empirical endpoints are based on, for example, visual acuity, while the more subjective endpoints include patient-reported outcomes (PROs) and recording of symptoms. In this article, we will discuss how biomarkers can be used to shorten or optimize drug development in a way that is acceptable to drug regulators, as well as other related questions, taking the European drug regulatory landscape into account. This information is aimed at academics, pharmaceutical companies both large and small, health care professionals, and patients. Such questions are increasingly relevant and important with increasing demand for earlier access to new, safe, and effective medicines, particularly for diseases with unmet treatment needs. Ophthalmology has many such indications for which there are no satisfactory methods for treatment or prevention of disease. There are also a number of slowly progressing ocular diseases for which markers of disease progression would be more or less necessary for the conduct of a clinical trial within a reasonable time frame. Other factors that make surrogates or biomarkers relevant in drug development are pressure on health care budgets, increasing costs of medicines, and a focus on precision or personalized medicines. Efficient streamlined drug development programs could avoid rising medicine costs stemming from wasteful approaches. Adopting novel approaches in drug development is not without risks to the developer if decision makers such as regulators do not agree with the approach taken. How can such risks be managed and minimized yet retain the potential advantages of surrogate endpoints or biomarkers, such as earlier readouts of efficacy or better detection of the optimum dose and safety, and at the end of the day, speed up patient access to new medicines?

This article will stress the importance of the proposed regulatory “context of use” of the biomarker. There will be a discussion of the process for gaining regulatory acceptance for such methods, the scientific expectations in terms of validation, the European conditional marketing regulatory framework wherein biomarkers or surrogate endpoints could be accepted in lieu of clinical outcome measures, and current and future use of biomarkers in drug development. Medical devices (including those for diagnostics) in Europe are subject to a separate legal framework and thus out of scope for this article.

CONTEXT OF USE

When proposing a biomarker in drug development, the starting point is the context of use—whether intended as a surrogate endpoint for clinical efficacy or otherwise. The nature, purpose, and techniques must be clearly defined. There are several common themes for biomarker use: it could aim to substitute for established visual function measures (visual field or visual acuity) or for functional vision (e.g., reading or navigation). Biomarkers could be used to identify a specific patient population or a subset of this population, for example,
TABLE 1. Principles for Validation of a Surrogate Marker of Visual Function

<table>
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<tr>
<th>Principle</th>
<th>Description</th>
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<tr>
<td>Plausibility</td>
<td>The marker should be mechanistically and/or biologically plausible. Credible mechanisms connect the marker, the pathogenesis of the disease, and the mode of action of the intervention.</td>
</tr>
<tr>
<td>Construct validity</td>
<td>Method for test and scoring must distinguish subject with normal visual function from those with impaired visual function. The marker should be able to measure seriousness in subjects with impaired vision and distinguish higher from lower performers.</td>
</tr>
<tr>
<td>Reliability</td>
<td>Performance of the marker should be evaluated. Interobserver, test-retest, and intraobserver reproducibility should be demonstrated.</td>
</tr>
<tr>
<td>Content validity</td>
<td>The marker should directly represent aspects of visual function (visual acuity, visual field, contrast sensitivity, color vision, dark adaptation), functional vision (e.g., reading, orientation mobility, activities of daily living, visual communication, and visual job skills), or vision-related quality of life.</td>
</tr>
<tr>
<td>Responsiveness/predictability</td>
<td>The marker should have the ability to detect a change. It should identify differences in scores over time in subjects whose visual function has changed and remain stable in subjects with a stable visual function. When aiming to substitute for an effect on visual function, the marker should be able to predict a future clinical outcome.</td>
</tr>
<tr>
<td>Change to intervention</td>
<td>The marker should demonstrate a change in response to the intervention in parallel with a defined visual function outcome.</td>
</tr>
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</table>

If the above principles have been appropriately investigated and demonstrated, the marker may be accepted to support regulatory decisions in the approval of a new drug. For a fully validated endpoint as a primary endpoint in a confirmatory trial, it must finally be demonstrated that the change can be concluded to represent or predict a clinical benefit across trials with other interventions.

Conditional Marketing Authorization and Use of Biomarkers as Surrogate Endpoints

At the time of the marketing authorization application (MAA) in Europe, regulators expect that the dossier should contain a thorough justification of the validity of the primary endpoint. However, the MAA could be based on surrogate endpoints that are reasonably likely to translate into a clinical benefit, but do not directly measure it. The suitability of the surrogate, ability to predict the clinical outcome, the level of certainty, and the evidence need to be discussed in the MAA submission. If the evidence fully supports the surrogate endpoint, then a full license, all other standards being met, would be expected.

From an ophthalmic perspective, we would want to know, for example, how the proposed surrogate endpoint translates into a delay to significant visual impairment or into a direct treatment effect.

Under the European regulatory framework, a conditional marketing authorization (CMA) could be possible when a biomarker shows, with reasonable certainty, benefits that outweigh remaining uncertainties about the extent to which the marker translates into a clinical benefit (as well as the risks). Thus, marketing is conditional on confirmation of the clinical benefits through specific obligations post authorization. In other words, the benefit to public health of the medicinal product’s immediate availability on the market outweighs the risks due to need for further data. The EMA guidance provides further information on the CMA eligibility criteria (e.g., aimed at treating, preventing, or diagnosing seriously debilitating or life-threatening diseases, emergency situations, or medicines for rare diseases).
primary efficacy for products centrally approved (1999–2016) for various ocular conditions in the EU.

As seen in the table, in pivotal registration trials, the evaluation of primary efficacy has been based on symptomatic improvement in allergic and dry eye conditions; however, so far, the only clinical primary endpoint that addresses visual function has been the evaluation of best corrected visual acuity (BCVA). Other functional measures such as visual field, contrast sensitivity, and photophobia were used as supportive endpoints in these studies. However, since generally accepted anchors (with exception of visual field where some consensus has been reached) to define relevant changes are not yet in place, their ranking as secondary or exploratory outcomes are appropriate.

In addition, there is some experience with the evaluation of diabetic retinopathy (DR) by use of the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale and this is briefly addressed in the label for Eylea (Bayer Pharma AG, Berlin, Germany). DR is also accepted as an outcome for various ocular conditions in the EU.

### Glaucoma

Owing to the generally slowly progressing visual field loss in glaucoma, a reduction in IOP has been the established efficacy measure in this therapeutic area for decades—even though the association between an IOP reduction in terms of visual field progression was not known. The work of Heijl and coworkers subsequent to the work of Heijl and coworkers, 5 nevertheless presented epidemiologic evidence demonstrating that a reduction of the IOP reduces the risk for a future visual field loss. Even though IOP is a key risk factor for glaucoma, some glaucoma patients still progress to vision loss despite low IOP; there is thus a need for alternative treatment strategies intervening at the level of retinal ganglion cells or the optic nerve. Consequently, there is a need to develop new surrogate markers for efficacy, but none is yet established. New structural and functional endpoints were discussed in a symposium gathering of the glaucoma research community and the United States Food and Drug Administration (FDA). 6 Also from an EU perspective, stakeholders are encouraged to bring forward proposals, for example, as requests for qualification advices for new markers (see below).
Uveitis

Also in uveitis, where the ultimate aim is to preserve vision, cells and flare for anterior uveitis, or vitreous haze for uveitis involving the posterior segment has been the basis of the license in registration trials. From an EU regulatory view, reassurance also in terms of preserving or (potentially) improving visual acuity is needed, but it is recognized that the evaluation of BCVA is too insensitive and not relevant for all patients. It is thus not regarded as an appropriate primary efficacy endpoint. Vitreous haze is associated with the inflammatory process and therefore served as a primary endpoint; however, in intermediate or posterior uveitis, the degree of vitreous haze does not necessarily correlate with inflammatory activity over the severity spectrum of the disease. Therefore, we encourage alternative approaches. While a final decision on the benefits of a new drug for the treatment of uveitis includes evaluations also of secondary endpoints that are expected to address other aspects of inflammation, a composite endpoint including such aspects as structural changes (e.g., macular edema, retinal vascular inflammatory changes) and patient’s symptoms may be useful for a more robust evaluation of a treatment effect in this rather limited, but highly heterogeneous, population. In this regard, the multicomponent strategy for primary efficacy (i.e., inclusion also of retinal inflammatory lesions and BCVA) used in the registration trials for Humira (AbbVie Ltd, Maidenhead, United Kingdom) in uveitis are acknowledged. As for glaucoma, EMA welcomes proposals for discussion on more optimized endpoints in uveitis.

Retinal Degeneration

In slowly progressing diseases such as dry age-related macular degeneration (AMD), retinitis pigmentosa (RP), or other slowly progressing inherited retinal diseases, clinical endpoints such as BCVA and visual field have clear limitations. These endpoints are recognized as not being sufficiently sensitive and thus not appropriate for evaluating efficacy, as the long duration of the trials and/or the high number of patients to be included could risk making the trial unfeasible. As discussed below, potentially, certain populations may be enriched to obtain more timely evaluations of a treatment effect.

In dry AMD with geographic atrophy (GA), there has been focus on anatomic markers as surrogates for clinical endpoints for some years. Structural markers include, for example, evaluations of the change in area of the GA or the volume of drusen. In several of the currently ongoing phase II/III interventional trials for GA, progression of the area of the atrophic lesion is assigned the primary outcome measure.

From the EU regulatory perspective, the use of GA area as a primary efficacy variable could in principle be acceptable. However, no primary outcome for efficacy has yet been validated for this condition in a licensing procedure and therefore, it needs to be justified that the marker represents a valid surrogate measure for visual function. Such justification could be based partly on literature demonstrating the prognostic value of GA area on visual function, but there would also be a need for support by evidence from the registration studies showing at least a trend of a positive effect of treatment on functional parameters. Secondary clinical meaningful outcome measures might include BCVA, contrast sensitivity, reading speed, perimetric measures, and PROs, among others. Importantly, the clinical meaningfulness of a change in the rate of progression of the lesion size in terms of delay to significant visual impairment remains to be justified.

Other structural markers under development include measurement of the ellipsoid zone (EZ) width or area disruption in patients with RP. EZ measurements have been investigated in RP patients and it has been shown that the measure is robust and that it changes over time, at least in subjects with X-linked RP.9 Other studies have been performed to correlate EZ measurements with visual field measurements,10,11 and it appears that the area around the edge of the EZ width represents the part of the retina that undergoes the most rapid rate of visual field loss.10,12 Thus, there is scientific support for the concept of developing the EZ measurement as an endpoint for use in drug development. However, besides some concerns regarding the manual procedure to identify the zone and its fuzzy borders, there is yet insufficient information to conclude whether the EZ is a suitable endpoint to demonstrate efficacy in RP patients. For a fully validated endpoint with the context of use as a primary endpoint in a confirmatory trial, it ultimately needs to be demonstrated that the EZ predicts change with the intervention and that this change can be concluded to represent a clinical benefit.

In 2016, the Innovative Medicines Initiative 2 (IMI2) decided to support the Macustar project, a project that aims to identify and validate functional, structural, and patient-reported endpoints for use in drug development in patients with intermediate AMD, that is, in subjects with impaired low-contrast and low-luminance vision, but not yet late-stage AMD with GA or neovascular disease. The project is still in an early phase, but future interactions with regulators are foreseen and welcomed.

Measuring not only visual function, but also functional vision, has an important place in drug development to evaluate or refine the risk/benefit ratio of intervention in patients with impaired vision. For example, in 2016 EMA published a letter of support for the development of reading speed and Functional Reading Independence (FRI) Index in patients with GA (Table 3). With the ongoing research progress, for example, in gene and cell therapy, there is need for further development of markers for efficacy, and there is promising work in progress. To capture aspects also of functional vision, mobility testing under well-defined and standardized conditions has the potential to serve as a future highly ranked endpoint in relevant settings, but there is currently insufficient regulatory experience; thus, it is premature to draw any conclusion on the adequacy of mobility testing for decision making with regard to patient benefit.

Patient-Reported Outcomes

Although clinical endpoints, new PROs, generally in the form of questionnaires, provide a direct report from the patient without interpretation by the clinician, and they could also be considered novel methods that need validation. The specific validation methods for PROs require separate detailed consideration and are not addressed here, but some regulatory considerations are worth mentioning. The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), a broad measure of visual functioning and quality of life, is the most commonly used PRO for ophthalmology and low vision patients.14 It is a generic instrument widely used in several ocular conditions. While the NEI VFQ-25 has been shown to be relevant and appropriate for use in patients with a number of conditions, it has also been criticized, for example, for floor and ceiling effects, and for not being appropriate in certain indications.15,16 It is also not disease specific. There are several additional ocular-specific PROs validated to a greater or lesser extent, but only occasionally seen in applications for approval of drugs in the EU. In addition to the FRI discussed above, additional instruments are under development. From the EU
Enrichment of a Study Population

Biomarkers have a place in drug development to enrich a study population for purposes of identifying a patient population that may progress more rapidly (based on prognostic biomarkers), detecting a (larger) treatment effect (based on predictive biomarkers) with consequential impacts on trial design. The evidence supporting such biomarkers will need to address regulatory questions, which often involve the rationale, the proposed cutoff points, the relationship with other risk factors, and the handling of multiplicity. Furthermore, sponsors will be required to justify the choice of population, the endpoints used, and overall interpretation of findings including replication.

In GA, disease characteristics such as bilateral GA or neovascular disease in one eye, a baseline BCVA of 20/50 or better, and hyperautofluorescence adjacent to the GA have been associated with a more rapid progression to loss of BCVA. When a population is enriched, the possibility of detecting a relevant treatment effect within a clinical trial of a reasonable duration may thus increase. Other approaches in GA as well as in other diseases include restricting or enriching the patient population to one with certain gene mutations associated with risks for development or progression of AMD. For example, in the ongoing development described for the complement factor D inhibitor lampalizumab, which is currently under evaluation in phase III clinical studies, the studies are enriched with “biomarker positive” subjects, that is, subjects who are positive for complement factor I (e.g., EudraCT No. 2014-000106-35).

As summarized in Table 4, in 2015, the EMA published a letter of support for the development of microaneurysm formation rate (MAFR) as a biomarker to enrich a type 2 diabetic clinical trial population with mild to moderate DR with those at higher risk of developing clinically significant macular edema.

Table 4. Letter of Support Issued by EMA for a Biomarker for Enrichment

<table>
<thead>
<tr>
<th>Biomarker/Novel Method and Need</th>
<th>EMA Review: Context of Use and Further Development Needs</th>
</tr>
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<tbody>
<tr>
<td>MAFR measured with a validated automated method</td>
<td>MAFR seems to be a very promising biomarker for enriching a patient population at higher risk for the development of CSOMO. Additional data are needed given the low CSOMO event rates in the validation studies, the highly variable progression rates between subjects, and to enable evaluation independently of other risk factors.</td>
</tr>
</tbody>
</table>

CSOMO, clinically significant macular edema.
Table 5. Previous Qualification Opinions

<table>
<thead>
<tr>
<th>Broad Purpose</th>
<th>Novel Method</th>
<th>EMA Review: Regulatory Qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome measure</td>
<td>The Paediatric Ulcerative Colitis Activity Index</td>
<td>Primary outcome measure in clinical trials of pediatric ulcerative colitis as a proxy for endoscopic assessment when colonoscopy is waived with appropriate justification among other regulatory uses</td>
</tr>
<tr>
<td>Prognostic biomarker</td>
<td>Total kidney volume</td>
<td>In combination with patient age and eGFR, as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease to identify patients likely to experience a progressive decline in renal function as characterized by a decline in eGFR or progression to end-stage renal disease</td>
</tr>
<tr>
<td>Proof of concept, selection of dose and treatment regimen</td>
<td>In vitro hollow fiber system model of TB</td>
<td>In anti-TB drug development programs as an additional and complementary tool to existing methodology to inform selection of dose and treatment regimen, providing preliminary proof of concept for developing a specific drug or combination to treat TB, and selecting the pharmacodynamic endpoints</td>
</tr>
<tr>
<td>Dose finding</td>
<td>Model-based design and analysis of dose finding</td>
<td>An efficient statistical methodology for model-based design and analysis of phase II dose finding studies</td>
</tr>
<tr>
<td>Disease progression model</td>
<td>Novel data-driven model of disease progression and trial evaluation in mild and moderate AD</td>
<td>As a longitudinal model for describing changes in cognition in patients with mild and moderate AD, and for use in assisting in trial designs in mild and moderate AD, to simulate the natural progression of disease (without placebo or drug effect), to inform on the power of competing designs</td>
</tr>
<tr>
<td>Enriching a clinical trial population</td>
<td>Cerebrospinal fluid biomarker signature based on a low Aβ42-4 and a high feA42</td>
<td>To identify patients with clinical diagnosis of mild to moderate AD who are at increased risk of having an underlying AD neuropathology, for the purposes of enriching a clinical trial population</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; eGFR, estimated glomerular filtration rate; TB, tuberculosis.

procedures, clinical development of diagnostic agents, and various aspects of pharmacogenomics in drug development. Any legal or natural person can apply, including consortia composed of any or all of the following: academics, companies, or patient organizations. We encourage such consortia to avoid multiple and divergent duplication of possible new endpoints and waste of resources. The outcome of the advice procedure is an advice letter to the applicant(s) providing the regulators’ opinion on the proposed plan. Obtaining such advice before embarking on a biomarker development plan and costly or lengthy studies represents a risk management approach that might otherwise not meet regulators’ expectations.

On the basis of the qualification advice, EMA may propose a letter of support as an option, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data. EMA will publish letters of support on the EMA website, subject to sponsor’s agreement to encourage data sharing and to facilitate studies toward qualification for the novel methodology under evaluation (see also Tables 3, 4).

Qualification Opinion

When sufficient information has been put together and the applicant considers that there is enough evidence to support the biomarker or surrogate endpoint for the intended context of use, then it is possible to submit the evidence dossier for regulatory acceptance in the process outlined in the above-mentioned guidance. Following evaluation, the EMA, in agreement with the applicant, will publish a draft opinion for public consultation on the EMA website to engage with broader scientific discussion; after review and resolution of comments, EMA issues a final opinion on the novel method.

Table 5 provides examples of novel methods that EMA has qualified for different contexts of use.

Conclusions

There is high activity in the development of drugs for ocular disease, an area with several conditions for which there is an unmet medical need. To date, while a number of surrogates for efficacy have been accepted by European regulators, the only functional clinical primary endpoint used for registration trials in Europe has been based on visual acuity. This is an endpoint recognized as not being feasible, for instance, in very slowly progressing diseases, or not even relevant for a number of conditions, and alternative endpoints are needed. Additionally, the use of new markers that, for example, capture a population that would respond better to treatment or one that responds sooner, is an area for further development.

To help speed up patient access to new medicines, there is consequently a need to explore the use of novel methods, biomarkers, and surrogate endpoints. However, the relevance of these methods needs to be justified with data and scientifically substantiated arguments. There is some flexibility in the European regulatory system to give timely access to new drugs for serious conditions for which there is a high unmet medical need; and a conditional marketing authorization based on a biomarker could be justified when the benefits, with reasonable certainty, outweigh the remaining uncertainties about the extent the biomarker translates into a clinical benefit (and the corresponding risks). Independent of the route to approval of a new medicine, the benefit/risk evaluation is based on all available data.

There is an EU regulatory pathway for the qualification of biomarkers or novel methods. A collaborative approach including academia, clinicians, and industry is encouraged. After advice has been received and the marker/method has been developed and validated, a qualification opinion could be sought. A positive qualification opinion will give the applicant regulatory acceptance for use of the marker in a defined context. Further requests for qualification advice (as well as opinions) in the field of ophthalmology with multiple interactions and dialogue are welcomed.

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References


