Dry Eye Disease:

Regulatory Requirements Differ Around the Globe – with Implications for Product Development and Patient Access.

A review of standards for new ophthalmic therapies in key pharmaceutical markets.

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List of abbreviations

AAO	American Academy of Ophthalmology
ADES	Asian Dry Eye Society
API	Active Pharmaceutical Ingredient
BVA	Bundesverband der Augenärzte Deutschlands e.V.
CMC	Chemistry, Manufacturing, Control
CMC/HPMC	Carboxymethylcellulose / Hydroxypropyl methylcellulose
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
DEQ-5	5-Item Dry Eye Questionnaire
DOG	Deutsche Ophthalmologische Gesellschaft
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IgA	Immunoglobulin A
LED	Light Emitting Diode
LFA-1	Lymphocyte function-associated antigen 1
MGD	Meibomian Gland Dysfunction
MMP-9	Matrix metalloproteinase 9
MOA	Mode of action
mOsm	Osmolality
MPA	Medical Products Agency
NCT	clinicaltrials.gov identification code
NDA	New Drug Application
OCT	Optical coherence tomography
OSDI	Ocular Surface Disease Index
OTC	Over-the-counter
PEG-400	Polyethylene glycol 400
PMDA	Pharmaceuticals and Medical Devices Agency
PPP	Preferred Practice Pattern
RASP	Reactive aldehyde species

SANDE	Symptom Assessment in Dry Eye Questionnaire
TFBUT	Tear film break-up time
TFOS	Tear Film & Ocular Surface Society
USA	United Stated of America
USD	US dollar
VAS	Visual Analogue Scale

1 Executive Summary

Dry Eye Disease (DED) is a common ocular surface disease affecting millions of people worldwide. Typical symptoms include ocular discomfort and visual disturbance, having significant impact on the patients' quality of life. The loss of homeostasis of the tear film leads to insufficient protection and therefore potential damage of the ocular surface. The current treatment options are limited and leave patients and ophthalmologists unsatisfied, resulting in a high unmet medical need. Additionally, increasing prevalence and several risk factors like aging population and screen work, make innovation and new treatment options necessary. But to date the available DED drugs are only approved in single key pharmaceutical markets.

To identify the underlying reasons for this observation, this thesis analyzed disease definition, market situation, diagnosis, and treatment guidelines as well as regulatory guidance for drug development in the key pharmaceutical markets United States of America (USA), European Union (EU), and Japan. Additionally, approved indications, clinical programs, and regulatory history of available DED drugs were analyzed.

The review showed that there is currently no common definition of DED in the different regions. In the USA and the EU inflammation is regarded as an essential part of the disease cascade and first focus of treatment, while the Asian definition considers tear film stability as the main component and focus of treatment.

The DED markets in all regions consist of two components: artificial tears and drugs. Although artificial tears are categorized differently as medical devices, over-the-counter (OTC) drugs or prescription drugs in the different markets, they generally serve as the first treatment option, often positively influencing subjective symptoms. Artificial tears are often easily available as OTC products, supporting self-treatment for milder versions of DED. The known effect of artificial tears complicates drug development as the efficacy of the active pharmaceutical ingredient (API) needs to be significantly greater than the vehicle, which is typically similar to artificial tears. This led to a high failure rate in clinical DED trials, resulting in several discontinued development projects in the past years.

Another aspect is the variety of diagnostic tools and outcome measures which are difficult to standardize and are associated with high variability. It remains debatable which level of

improvement in a certain parameter is clinical meaningful, which further complicates harmonization. This might be a major reason for the variability in regulatory requirements in the geographies. The US FDA accepts for example studies with 1 day treatment duration if a significant improvement over vehicle can be demonstrated in signs and symptoms of DED. However, the European expectations are that treatment of a chronic disease like DED requires chronic treatment and persistent effect, so that effect demonstration after 6 months treatment period is recommended.

The comparison of available DED drugs showed that the products are approved for different indications like “Increasing tear production” or “treatment of signs and symptoms of DED”. While drugs targeting inflammation, like Restasis®, Ikervis® (both cyclosporine) or Xiidra® (lifitegrast), are available in the US and the EU markets only, mucin secretagogues, like Mucosta® (rebamipide) or Diquas® (diquafosol), are the only approved drugs in Japan (besides artificial tear products). The analysis revealed that clinical programs often required several trials to show the desired effects. Approval of formally not met primary endpoints in single regions lead to non-acceptance of the dossiers in other regions.

With increasing prevalence, medical need, and public interest further initiatives for harmonization of a common understanding of DED are expected. Additionally, identification and validation of robust clinical (bio-)markers for indicating disease severity and treatment effects will further help to promote harmonization of regulatory requirements. In conclusion, innovation is needed to better understand DED, and as a consequence bring regulatory agencies to common accepted standards and finally patients worldwide to new treatment options to improve their quality of life.

2 Introduction

Healthcare is one of the most regulated industries in the world [1]. On the one hand, governmental regulatory authorities are setting high ethical and regulatory bars for existing and new medicines to ensure patients' safety and effectiveness of medicinal products [1]. On the other hand, developing new medicines requires high out-of-pocket expenses, long overall development times and bears significant risk of failure [2]. This requires entrepreneurship, solid companies, and potent investors. These counterparts set the basis of a dynamic area with tension between commitments to adequate standards to satisfy highest safety expectations and economical-oriented interests which also drive innovation [1].

Pharmaceutical development may vary substantially across therapeutic areas, but development costs for a new chemical entity or new biological substance from screening to market approval are estimated on average with approximately 1.3 billion US dollars in the period between 2009 and 2018 [2, 3]. These numbers also include the countless compounds which failed during the development [3]. There is a high variability in cost for each individual drug because of considerable variation in three key variables: success rates, development times and out-of-pocket expenses.

Significant investments and time are required to demonstrate quality, safety, and efficacy of a new medicine in a variety of critical areas: Chemistry, Manufacturing and Control (CMC), non-clinical and clinical studies to comply with regulatory standards and ensure patients' safety. Commercial success of the medicinal product and corresponding return of investment is usually only expected years after approval. Pharmaceutical companies often pursue a strategy to enter large indications or adding new indications to the drug's profile during its life cycle to reduce their risk [1]. It is further a common strategy to set up global development programs to be able to bring the product to market in various countries in a shorter period of time [1]. Economically large pharmaceutical markets like the United States of America (USA), the European Union (EU), and Japan are of high interest and often the primary focus of regulatory strategies [4]. Global drug development remains a common practice in the majority of medical indications [1]. Approval in key markets, like the USA or the EU, are also sometimes a prerequisite for approval in smaller countries which partially rely on the assessment of large stringent regulatory authorities [5].

The concept of global development is also common in Ophthalmology, particularly in key indications like intraocular hypertension (glaucoma) and retinal diseases. Contrary to the typical global development approach, in Dry Eye Disease (DED), a common ocular surface indication affecting tens of millions of people worldwide, only regional products dominate the respective markets [6]. So far, no medicinal product treating DED was yet approved in all of the key pharmaceutical markets. Although global product campaigns have been attempted by various, also large international pharmaceutical companies, their strategies were not successful, resulting in approvals in single markets only and several withdrawals of marketing authorization applications in key geographies for the same product using the same or similar datasets (section 6).

In summary, this results in highly diverse regional DED markets around the globe and particularly limits innovation in the respective countries and patients access to novel approaches and developments to treat this condition. The current treatment options are therefore limited and leave patients and ophthalmologists unsatisfied, resulting in a high unmet medical need [7]. Additionally, increasing prevalence and several risk factors like aging population and screen work, make innovation and new treatment options for DED necessary [8]. This further raises the question what potential barriers prevent or complicate classical, global developments for DED.

2.1 Objective

The objective of this thesis is to analyze the current situation of DED markets in three regions, which represent major pharmaceutical and ophthalmic markets: the USA, the EU and Japan [9]. The respective definition of the disease, diagnostic tests, outcome measures, and medical treatment guidelines, as well as currently available products on the respective markets are analyzed. A particular focus will also be laid on regulatory requirements for clinical DED drug developments, including analysis of regulatory guidelines, clinical trial packages from approved DED drugs as well as information from withdrawn marketing authorization applications.

The thesis finally summarizes and compares the differences with regards to the requirements for clinical development in the DED indication and proposes possibilities to

promote harmonization efforts to support global product developments and finally the availability of effective treatments for dry eye patients worldwide.

3 Background and Overview

Dry eye disease (DED), also called keratoconjunctivitis sicca, is a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film and accompanied by symptoms such as ocular discomfort and visual disturbance [10]. It is expected that 1.4 billion people worldwide have symptoms of DED [9]. The prevalence was shown to steadily increase, and is higher with age, in women and the Asian population [8].

3.1 Importance of the Tear film

DED is directly linked to the tear film of the eye. It is therefore important to understand its composition, the associated glands of the outer eye and its functions. It is suggested that the tear film can be differentiated into two different segments: the hydrated mucus layer and the lipid layer (Figure 1) [11].

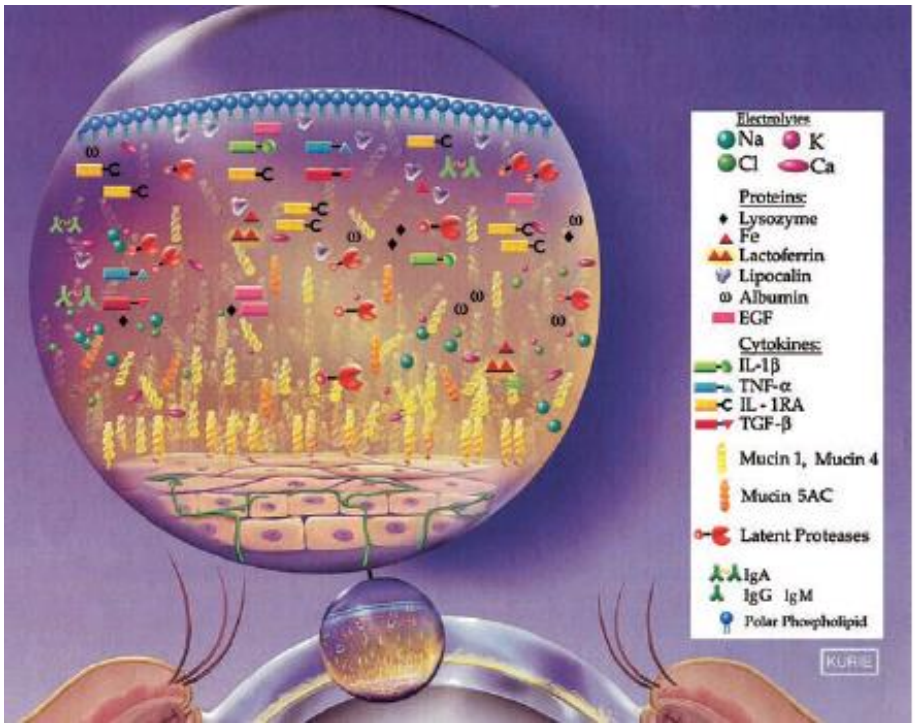

Figure 1: The normal tear film and its components [12]

The hydrated mucus layer is typically around 4-5 µm thick and consists mainly of an aqueous fluid that includes a variety of electrolytes, proteins, and mucins, a family of high molecular weight, heavily glycosylated proteins (glycoconjugates) [13]. This layer serves to

maintain the barrier function, hydration, and wettability of the hydrophobic surface of epithelial cell membranes and minimizes friction from blinking [13]. Mucins are produced by corneal and conjunctival epithelial and goblet cells [13]. The aqueous fluid provides the majority of the tear volume and is produced by the lacrimal glands [13].

The tear film lipid layer, typically 0.02 - 0.2 µm in thickness and primarily derived from secretes of the Meibomian glands, serves as the interface between the aqueous layer and the air [14, 15]. Tear film lipid layer is composed of a thin section of polar lipids interfacing with the underlying hydrated mucus layer and a thicker section of non-polar lipids at the air interface [14, 15]. The lipid layer functions as a smooth optical surface, reduces surface tension of the tear film and evaporation of aqueous tears [14, 15].

The normal tear film contains a tightly balanced complement of its components to allow fulfillment of its function [16]. One of the most important functions of this primary optical surface of the eye is to ensure proper vision [16]. The tear film is under constant 'stress' due to blinking which is an essential function of the eye helping to spread tears across and remove irritants from the surface of the cornea and conjunctiva [17]. Healthy adults blink between 10 to 15 times per minute. Every blinking puts the tear film into turbulence with the ability of the components of a healthy tear film to return to stable and structured tear film in a very short time [17].

The tear film further assures eye comfort through its lubricative properties which decrease shear forces from the lid margin during blinking [18]. Another function of the normal tear film is protection of the ocular surface epithelium from the typical daily environmental influences [19, 20]. These include microbes, pollutants, allergens, and adverse environmental conditions, such as low humidity and air movement from wind or air condition [19, 20]. This is accomplished through appropriate secretion of tear-containing protective factors like hydrating glycoproteins and antimicrobials (e.g., IgA, lactoferrin, lysozyme and defensins) [19, 20].

3.2 Dry Eye Disease (DED)

3.2.1 Disease Definitions

There is currently no single globally accepted definition of DED available. However, with increasing public interest and understanding of DED as a serious chronic or progressive

disease rather than a temporary syndrome, the scientific community from all over the world has increased their efforts to come to a more common understanding and definition of DED in recent years. One way to achieve this was the Dry Eye Workshops (DEWS™) I and II of the Tear Film & Ocular Surface Society (TFOS) which has issued their recent definition of DED in 2017:

"*Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles*." [21]

This definition already indicates that DED is typically a highly variable disease with multiple factors contributing to the disease pattern. Most countries or regions derived the definition from the DEWS II 2017 as the basis for their country-specific guidance and directly or similarly adopted the definition. In Germany, as an example for the EU, the definition is exactly translated into the German treatment guidance: Sicca Leitlinie 2019 [22].

The American Association of Ophthalmology (AAO) similarly defines DED as: "[…] *a group of disorders of the tear film that are due to reduced tear production or tear film instability, associated with ocular discomfort and/or visual symptoms and inflammatory disease of the ocular surface*." [23]

In both definitions, inflammation is considered to play an important role of the disease. Although the DEWS II report mentions that clinical manifestation of inflammation is not required to diagnose DED [21].

The Asian Dry Eye Society (ADES) defines DED quite different and more general: "*Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage."* [24].

This ADES definition is explicitly not following the inflammation-driven approach and rather focusses on the tear film composition [24]. Although the Consensus Report of the ADES specifically mentions that inflammation is an important risk factor or even a consequence of DED, it is assumed that inflammation is not the central core mechanism of DED and should therefore not be included in the definition [24]. This marks a key differentiator to the disease definitions in the EU and the USA.

Another concept that illustrates the complexity of DED as well as the involved pathologies is the Vicious Circle of DED Pathology developed by Baudouin et al 2016 (Figure 2) [25]. It shows that many of the different clinical observations directly influence each other and it summarizes the possible risk factors or other underlying diseases which can trigger DED [25].

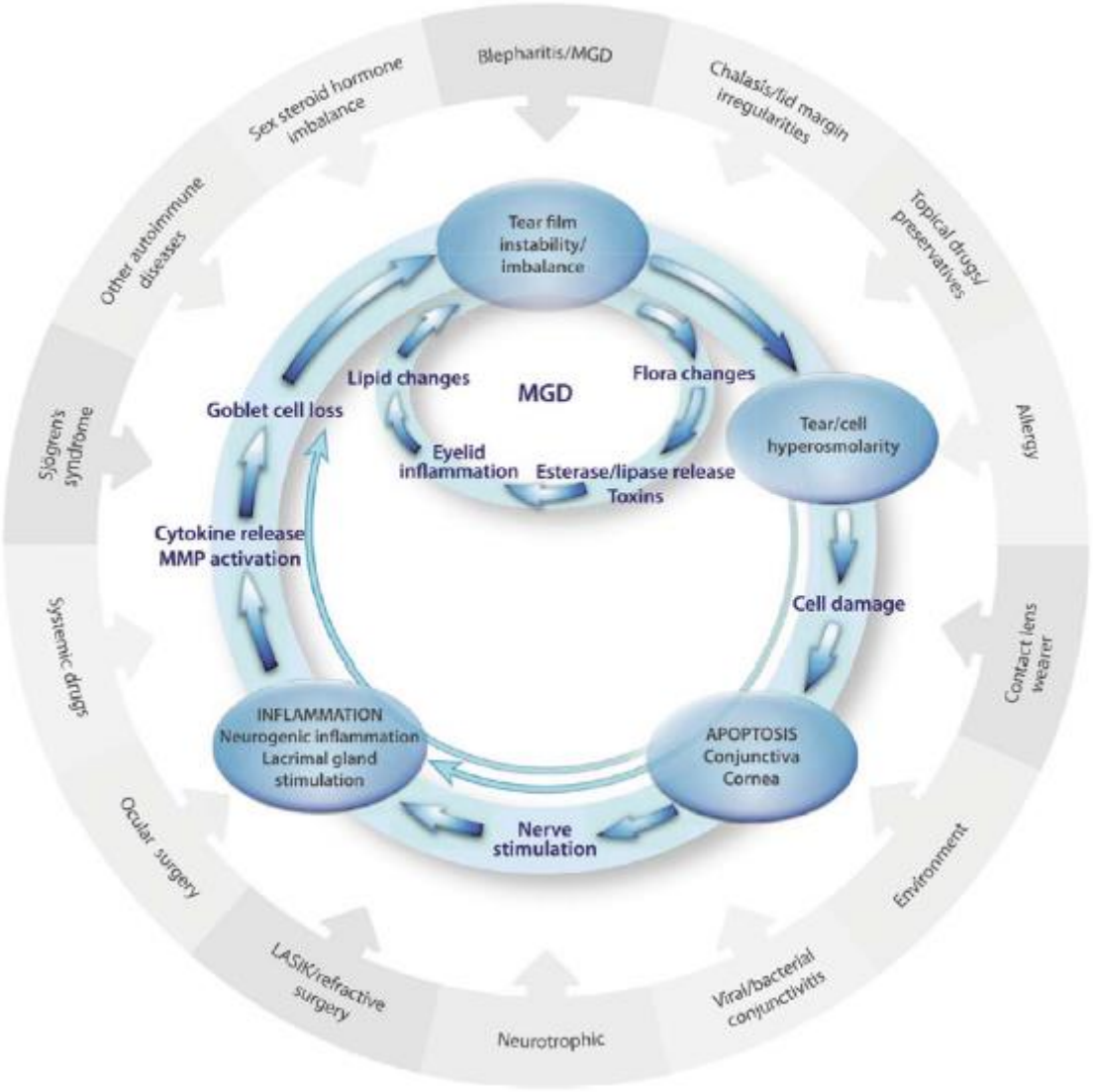

Figure 2: Vicious Circle of the Pathology of Dry Eye Disease [25]

3.2.2 Types of DED

DED is typically divided into two general subtypes: the aqueous deficient-type and the evaporative-type of DED as displayed in the Vicious Circle of DED model (Figure 2) [21, 25]. Both types are not fully independent from each other and often exist in mixed forms with one type often dominating [21]. Aqueous deficient DED is characterized by a reduced tear

production, due to e.g., dysfunctional lacrimal glands, which then leads to a reduced aqueous tear or increased osmolarity of the tear film and finally to an insufficiently protected ocular surface [21]. Evaporative DED is characterized by rather normal aqueous tear production, but pathologically increased evaporation of the tear fluid [21]. The lipid part of the tear film provides a natural barrier for excessive tear evaporation [21]. A reduced or porous lipid layer does not sufficiently prevent aqueous tear evaporation [21]. Evaporative DED is often associated with a Meibomian Gland Dysfunction (MGD) as secretion from the Meibomian glands is the sole natural source of the lipid layer [21]. Epidemiological studies demonstrated that evaporative DED or mixed forms are representing more than 80% of all DED cases [26].

Both types of DED result in tear film instability and consequently in ocular surface damage as the eye surface is not adequately protected against blinking and environmental stress [21]. The clinical experience and respective treatment guidelines also suggest that DED patients cannot be adequately treated with one universal therapy but require specific treatment for their individual type of DED and the resulting condition [23].

3.2.3 Symptoms and Signs of DED

Dry eye disease is often described by subjective patient-reported symptoms and objective clinical signs.

Symptoms of DED include feeling of dryness, burning, stinging, sandy/gritty sensation, foreign body sensation, itchiness, pain or photophobia [21]. These symptoms can prevent patients from carrying out basic activities of daily living such as reading, watching television, driving, and working [8]. In addition, symptoms impacting visual function such as fluctuating vision with blinking, blurred vision, and difficulty of reading are an important and yet underestimated aspect of the disease [8]. In consequence, DED negatively impacts quality of life comparably to other severe diseases [27] and adverse effects on mental health, such as depression and anxiety, have been observed [28]. Most patients consult a physician because of their dry eye symptoms or are diagnosed at eye doctor visit scheduled for other reasons [29, 30].

Subjective symptoms of DED are typically assessed by standardized symptom questionnaires [31]. Several accepted and validated questionnaires are available, which are

used in both, clinical practice for individual patients and for drug development [31]. The questionnaires often sum up to a score, which can be compared to healthy scores [31].

The most widely used questionnaire for DED is the Ocular Surface Disease Index (OSDI, Allergan) [31]. It measures frequency of experienced symptoms, environmental triggers and vision-related quality of life. OSDI scores of 13-22 indicate mild DED, 23-32 moderate DED and ≥33 severe DED [31]. Another common questionnaire is the 5-Item Dry Eye Questionnaire (DEQ-5) which is characterized by a shorter length and its discriminative ability [31]. DEQ-5 scores of ≥6 indicate DED, whereas a score of ≥12 indicates a Sjögren syndrome, a serious systemic disease resulting in inflammatory cellular infiltration of the exocrine glands (including lacrimal glands) which leads to saliva- and tear-production deficiency [23, 31]. Another widely used questionnaire is the Symptom Assessment in Dry Eye (SANDE), a short questionnaire based on visual analogue scales (VAS) that quantifies both severity and frequency of dry eye symptoms [31].

All these questionnaires have been used in clinical trials and drug development but could often not show treatment effects successfully [31]. Therefore, companies have started to rather use the Dryness Score or Discomfort Scale which is focusing on single symptoms. This was already successfully included in clinical development of approved US products (see section 6).

In addition to the subjective symptoms, there are a number of objective DED clinical signs which can be examined by a physician only. The most common signs and corresponding tests are briefly explained here exemplary to give an impression of available diagnostics and outcome measures:

Tear film stability

- Tear film break-up time (TFBUT): TFBUT is determined after instillation of a fluorescein drop using a slit lamp with cobalt blue filter. After a blink the time until the break-up of the tear film is measured. TFBUT is often reduced in DED patients, a time < 10 seconds is considered the cut-off for DED diagnosis. [26, 31, 32]

Tear volume

- Tear film meniscus: can be observed during slit lamp examination or with Optical Coherence Tomography (OCT) and is often reduced in patients with aqueous deficient DED [26].
- Tear secretion test: The Schirmer tests measures the secretion of the lacrimal glands. A filter strip is placed in the conjunctival sac of the lower lid and the meniscus increase is measured after 5 minutes. Variability is typically high in Schirmer results due to reflex tearing, but overall results are reduced in aqueous deficient DED patients. Several cut-off values have been used, from ≤ 5 mm/ 5 min to ≤ 10 mm/ 5 min. [26, 31]

Tear film composition

- Tear film osmolarity: is measured with an osmometer. It is expected that osmolarity is changed in DED patients due to different tear composition. An osmolarity ≥ 308 mOsm/L is considered an indicator for DED. [33]

Damage to ocular surface

- Examination of the ocular surface is performed with a slit lamp, often supported by dyes. Fluorescein stains the precorneal tear film and the epithelial erosions in the conjunctiva and cornea. [31]
- Lissamine green stains devitalized and membrane-damaged cells indicating damage to the ocular surface. [26, 31]

  The staining with fluorescein or lissamine green is then assessed using different grading scales, like the Oxford scale, the NEI scale, or the proprietary scale from the clinical contract research organization ORA. [31]
- Conjunctival folds: Temporal lid-parallel conjunctival folds (LIPCOFs) in straight gaze are a result of increased friction between the lids and the conjunctiva. They are regarded as an important indicator of DED [26, 34]. A cut-off value of 2 is typically used [31].

Inflammation of the ocular surface

- Ocular or conjunctival redness: is an indicator of an inflammation and can be assessed with a pen torch or standard slit lamp biomicroscopic examination. For quantitative documentation digital imaging analysis methods are available. [31]

- Matrix Metalloproteinase-9 (MMP-9): is measured in a tear film sample and is deemed to be an adequate indicator for ocular inflammation [35]. Levels > 40 ng/mL indicate DED [31].

Eye lid aspects

- Meibography: allows observation of the silhouette of the meibomian gland morphological structure. Different devices are available using infrared LEDs with an infrared camera. [31]
- Lid closure: insufficient lid closure can disturb the integrity of the tear film [26].
- Blink rate: reduced or incomplete blinking is typical in DED patients, especially during reading or computer work blink rate can be significantly reduced [26, 36].

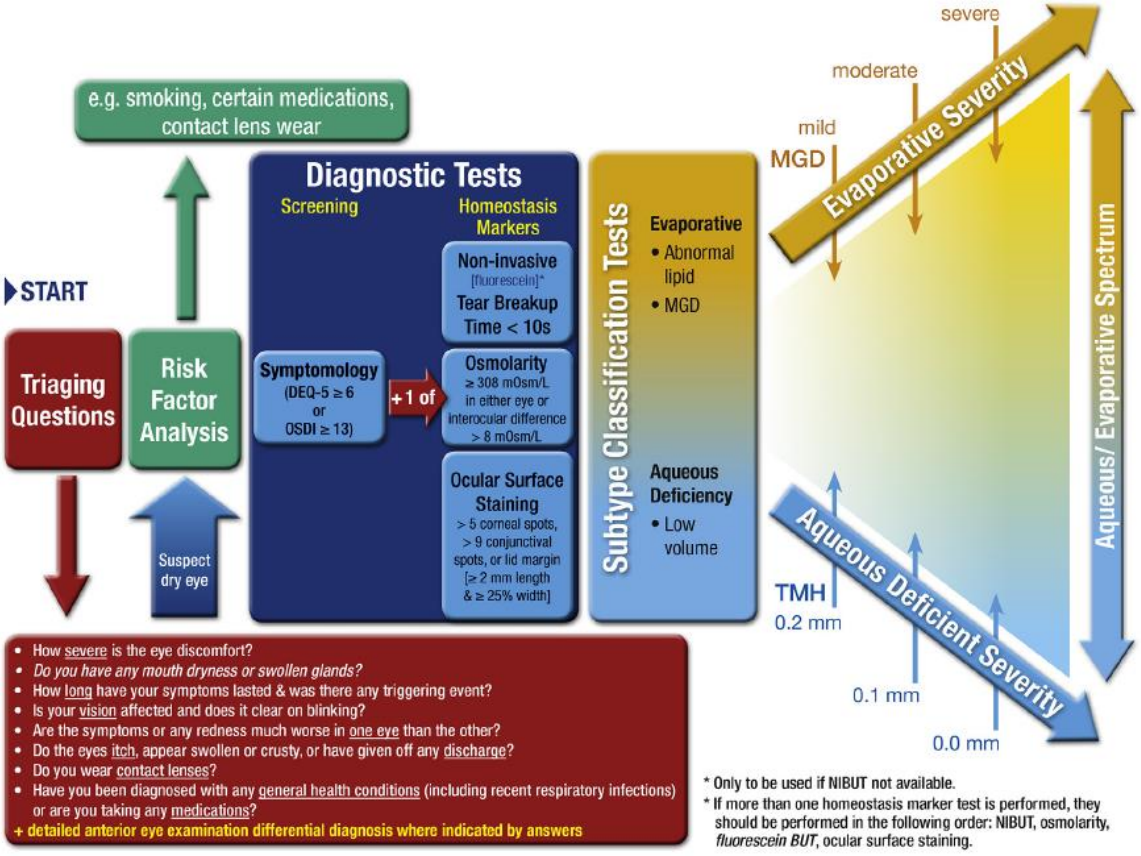

Figure 3: DED diagnostic test battery according to DEWS 2017 [31]

Careful evaluation of presented signs and symptoms is then required to determine a DED diagnosis [31]. The diagnostic test battery presented in the DEWS II report (Figure 3) shows that precise DED diagnosis is challenging as there are various forms of DED manifestation [31]. However, both parameters, meaning signs and symptoms, need to be fulfilled to

clearly diagnose DED [31]. Nevertheless, signs and symptoms often do not directly correlate in DED, which also presents a major challenge for clinical development [31, 37].

On one hand, there can be asymptomatic patients with clinical signs, potentially due to predisposition to DED or dysfunctional sensation [21]. On the other hand, there are symptomatic patients which present no clinical signs of DED either due to the state being rather sub-clinical in severity or due to a neuropathic pain [21]. An additional challenge are comorbidities, e.g., different diseases like allergies or ocular infections with similar clinical presentation but different root cause that require different treatments (see also Figure 2) [21].

DED is also often categorized by severity level, which especially plays a role in the selection of the best and appropriate treatment [26]. The typical three categories are mild, moderate, and severe DED [26]. A more comprehensive table was presented in the 2007 TFOS DEWS I report [38], summarizing the severity of the different observations for the DED categories (Figure 4).

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/−	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓meniscus	Filamentary keratitis, mucus clumping, ↑tear debris	Filamentary keratitis, mucus clumping, ↑tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratiniza-tion, symblepharon
TFBUT (sec)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

* Must have signs AND symptoms.

TBUT, fluorescein tear break-up time; MGD, meibomian gland disease.

Figure 4: DED severity grading scheme [38]

Mild DED forms are characterized by mild and episodic visual symptoms, none to mild corneal and tear signs, and variable TFBUT and Schirmer score [26]. Moderate DED is characterized by more annoying visual symptoms, mild or variable corneal and tear signs, faster TFBUT and lower Schirmer score, respectively [26]. Visual symptoms which are

persistent or chronic and start to limit activities point then to a severe type of DED, often accompanied by severe corneal and tear signs, including keratitis and very fast TFBUT (≤5 sec) or low Schirmer score (≤5 mm/5 min) [26]. However, a severity categorization is not included in the 2017 DEWS II report anymore.

3.3 Epidemiology

Population-based surveys indicate that DED affects millions of people worldwide. Market Scope estimated 1.4 billion DED patients in 2019 [9]. In the USA 17 million patients have been diagnosed with DED [9]. As many as 5 - 35% of patients visiting an ophthalmology clinics report DED symptoms, making it one of the most common conditions seen by ophthalmology specialists [29, 30]. Prevalence is greater in females and elderly subjects. Schaumberg et al. reported prevalence rates in the US range from 3.9% in men aged 50–54 years to 7.7% in those 80 years or older, rates increase from 5.7% in women younger than 50 years to 9.8% in women >75 years [39, 40].

For the EU exemplary numbers for Germany back from 1977 show that 11.7% of Germans suffered from DED [41]. Market research in 2019 estimated that 57.8 million people were diagnosed with DED in Western Europe, in addition to a high number of people with pre-clinical symptoms but no objective clinical signs (Market Scope DE Report 2019). A recent publication estimates prevalence in Europe at 16.4% [42].

Prevalence is also affected by geographical parameters and appears to be higher in the Asian population with an estimated prevalence of 27.1% [42]. A large, population-based study of DED in Japan revealed clinically diagnosed DED to be 2.1% in men and 7.9% in women [43]. The prevalence of severe symptoms of DED in men and women were 11.5% and 18.7%, respectively [43]. The prevalence for the combination of clinically diagnosed DED and severe symptoms of DED in men and women were 12.5% and 21.6%, respectively [43].

Moreover, DED provides a substantial economic burden for societies in developed countries, with estimated direct annual costs for the health care system of almost 4 billion USD in the USA [44]. The average annual direct medical costs per patient increase by a factor of 2 from patients with mild to severe DED symptoms [44]. For 2008, the average annual indirect DED costs to society were estimated at 11,302 USD per patient due to

reduced productivity, adding up in total to about 55.4 billion USD for the US alone [44]. The reduction in productivity and the number of affected days is linked with the increasing severity of DED symptoms, as shown by number of days absent from work and days of reduced productivity while at work, with 8.4 to 14.2 days and 91 to 184 days, respectively [44].

4 Challenges in Dry Eye Treatment

DED is a common condition affecting millions of people worldwide, making it a considerable disease with significant impact on quality of life and economics [9]. It is evident that the DED prevalence is increasing with risk factors like an aging population, increased screen work / time, continuing urbanization, and growing affluence in developing countries [8]. This brings DED increasingly to public as well as scientific attention.

There is still a high unmet medical need in DED with patients and ophthalmologists being unsatisfied with the currently available treatment options [7]. Historically, DED was for a long time not perceived as a serious disease, but rather a subjective temporary condition [21]. This has certainly changed within the last years, especially with the TFOS DEWS I and II, bringing international specialists together to discuss a common understanding of the disease and underlying conditions. But in fact, DED still remains a quite new research area for the broader pharmaceutical industry [45].

One important challenge is that DED is a complex disease with different contributing factors and different clinical manifestation (see section 3.2) [21]. This also complicates systematic research, design of clinical trials and finally regulatory approval processes. While in other ophthalmic diseases like glaucoma the treatment focusses on one specific aspect like intraocular pressure (IOP) reduction, this is not the case in DED. The symptoms of DED are basically the most disturbing component for patients [21]. But these are subjective and evolve over time, while the underlying root-cause is often not clearly detectable, resulting in primarily symptomatic treatment approaches.

Another point is that artificial tears, which are a substantial part of DED treatment options, are mainly available as OTC products on the respective markets (see section 5), so that patients with milder or new DED symptoms, first start with self-treatment of widely available OTC products [23, 46]. In most cases, patients are expected to see an

ophthalmologist if more severe symptoms appear, or artificial tears do not provide symptomatic relieve to an acceptable degree [46]. As artificial tears present a proven treatment option for DED patients to improve symptoms (but not clinical signs), new therapeutic products need to take the hurdle to perform substantially better than the artificial tears [46, 47]. Artificial tears are often effective in treating certain symptoms although they do not include classical active pharmaceutical ingredients (APIs), and head-to head comparisons in clinical DED trials presents a major challenge that resulted in a high failure rate and several discontinued projects [47].

In addition, the available diagnostic tools and outcome measures (described in section 3.2.3) revealed to be highly variable, resulting in inconsistent observations in clinical development in the past [48]. This also complicates clear and harmonized regulatory requirements which appeared to vary in the different geographies and led to very different DED markets and treatment options for patients. The differences of the key pharmaceutical markets USA, EU, and Japan will be further examined in the following chapter.

5 Current situation

5.1 Classification of DED treatments

There are generally two different classes of DED treatments: artificial tears or lubricants and prescription drugs [23]. While artificial tears treat subjective symptoms of DED, DED drugs are thought to treat both signs and symptoms of DED.

Especially artificial tears are classified differently in the different regions:

In the USA, besides the prescription drugs, artificial tears are approved as OTC drugs [49]. There are also medical devices (510k submission) available, but these are only indicated for use as contact lens re-wettening agents. In the EU, artificial tears and contact lens re-wettening agents are typically classified as medical devices which are then available as OTC products [9]. In some EU countries, e.g., in France, certain artificial tear products can also be prescribed and are reimbursed similarly to the available prescription drugs. In Japan, artificial tears are approved as drugs, similarly to the USA [9]. Products containing sodium hyaluronate are approved as prescription drugs and are not available OTC. However, there

is also an OTC non-reimbursed market existing for lubricating eye drops and re-wettening agents for contact lens wearers [9].

Interestingly, despite the different categorization, the regulatory pathway for artificial tears is clearly regulated in all these geographies outlined above. Main criteria are clinical safety and improvement of symptoms which need to be demonstrated in clinical trials, typically without a comparator [49]. If known, registered substances are used for artificial tear products often no specific clinical data for the new product is required for product approval. Especially in the EU, this might be subject to change with the introduction of the new Medical Device Regulation. For specific DED treatments, which are expected to treat both signs and symptoms, regulatory requirements for clinical development are stricter and appear to be more diverse in the analyzed pharmaceutical geographies as detailed in section 5.4.

5.2 Dry Eye Market

The global DED market was estimated at 4.5 billion USD in 2020, covering prescription drugs, OTC drugs and medical devices [9]. This makes DED the 3rd biggest indication of the overall ophthalmology market with glaucoma revenues of 4.8 billion USD and retinal diseases accounting for 14 billion USD [9]. The biggest segment of the DED market are artificial tears which make up for more than 50% market share with estimated 2.6 billion USD [50]. This is followed by drug products including cyclosporines, LFA-1 antagonists, mucin secretagogues, and corticosteroids [50]. It should be noted that some pharmaceutical products are only available in single markets, e.g., LFA-1 antagonists are only approved in the US and mucin secretagogues only in Japan and some smaller Asian markets [50].

Regarding sold units, OTC products including artificial tears, are dominating the worldwide market with approx. 558 billion units compared to approx. 54 billion units for prescription drugs [9].

5.2.1 USA

The USA is the biggest DED market in terms of revenues and accounted for approx. 40% of the global market in 2020 [9]. The biggest shares belong to artificial tears and cyclosporine [9]. Artificial tears which are approved and commercialized as OTC medicinal products in

the US had a market share of approx. 42% in 2020 [9]. When comparing volumes, the USA is not the biggest market in the world accounting for approx. 83 billion sold units of DED treatments in 2020 [9]. OTC products are by far mostly used with approx. 77.8 billion sold units in 2020 compared to approx. 5.5 billion units of prescription drugs [9].

In the US, artificial tears can be classified in two categories: Polyethylene glycol (Peg-400)/propylene glycol-based and Carboxymethylcellulose/Hydroxypropyl methylcellulose (CMC/HPMC)-based [9]. Contrary to the other markets there are currently no sodium hyaluronate products available on the US market due to regulatory hurdles. Main brands in the market include Systane® by Alcon, Refresh® by Allergan or Visine® by Johnson & Johnson [9].

The dominating prescription drug is a cyclosporine product with an estimated market share of approx. 46% in revenue in 2018 (Figure 5) [50]. Restasis® (Allergan) is a 0.05% cyclosporine eye drop product and the first in market DED drug for almost two decades, with sales of over 1 billion USD in 2018 [50]. The second prescription drug with a significant market share of approx. 14% in 2018 is the LFA-1 antagonist lifitegrast (Xiidra®, Novartis), which was launched in 2016 and is expected to grow in the coming years based on its differentiated product profile compared to Restasis [50]. Corticosteroids and other drug classes accounted for approx. 2% market share in 2018 and are used to treat general ocular inflammation not specifically associated with DED [50].

Recently two new drugs for DED treatment have been approved: Cequa™ (Sun Pharma), a cyclosporine 0.09% microemulsion with a similar profile as Restasis and Eysuvis™ (Kala Pharmaceuticals), a corticosteroid eye drop using 0.25% loteprednol etabonate, approved for a short-term treatment of up to 2 weeks [9]. Both products only own small shares of the US DED market due to their recent introduction [9].

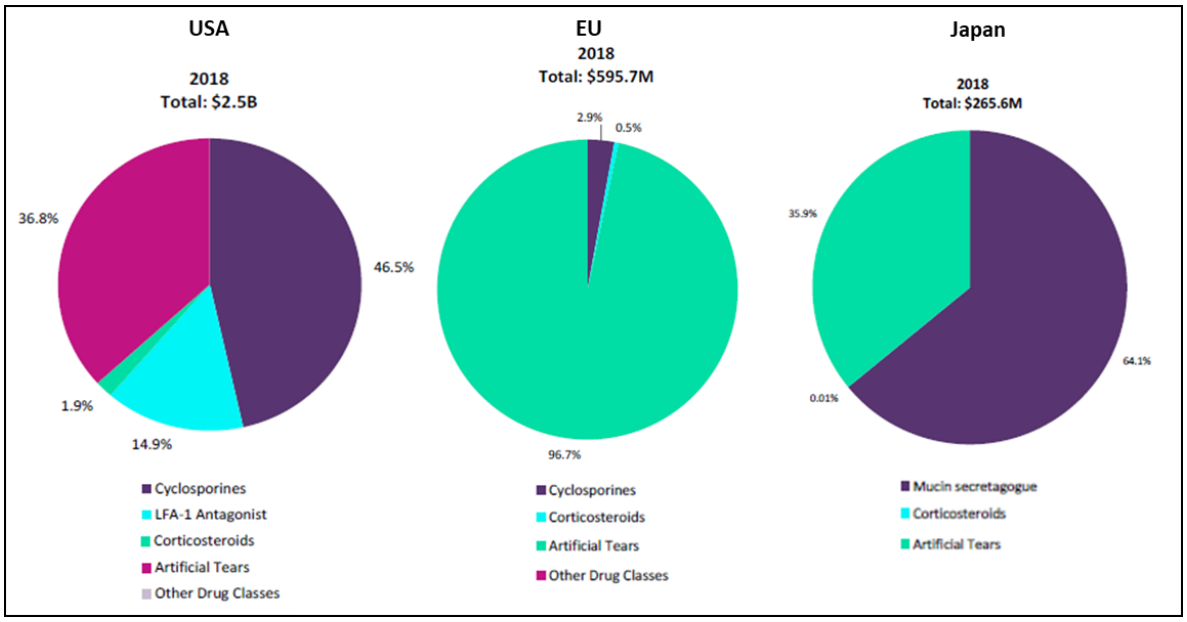

Figure 5: Drug sales by class for DED in the USA, EU and Japan in 2018 [50]

5.2.2 EU

In the EU, artificial tears dominate by far the DED market with approx. 96.7% market share in 2018 (Figure 5) [50]. In terms of volume, approx. 102 billion units of OTC products were sold compared to approx. 2.8 billion units of prescription drugs in 2020 [9].

Artificial tears in the EU are typically sodium hyaluronate-based, CMC/HPMC-based or Peg-400/propylene glycol-based [50]. These eye drops are CE-certified medical devices in the EU and are usually available as OTC products. Leading brands or product families are often from local manufacturers (e.g., Hylo-Comod® by Ursapharm) while global brands like Alcon's Systane®, or Allergan's Optive® are less dominant [50].

In contrast to the US, only one drug for the treatment of severe keratitis with DED in adults is approved in the EU: Ikervis® (Santen), a cyclosporine 0.1% eye drop. This treatment only represented about 2.9% of the EU DED market in 2018, likely due to the restricted indication [50]. Corticosteroids, like dexamethasone or prednisolone, are prescribed more widely than in the US, but their market share of approx. 0.5% is still rather small [50].

5.2.3 Japan

Japan is by far the biggest DED market in volumes of prescription drugs with approx. 33 billion units sold in 2020 [9]. Artificial tears account for about 50% of the DED treatments [50]. It should be noted that artificial tear products are approved as drugs in Japan [50].

Hyalein, a sodium hyaluronate artificial tear eye drop, is a generic prescription drug, comparable to medical device products in the EU [50]. Regarding other products, the situation in Japan is very different from the US and the EU [50]. There are no cyclosporine products approved in Japan yet, but two mucin secretagogues are available on the market, Diquas® (3% diquafosol, Santen) and Mucosta® (2% rebamipide, Otsuka Pharmaceuticals), which are intended to promote mucin production and are expected to increase tear film stability [50]. These products are available solely on the Japanese and few Asian markets [50].

In 2018 it was expected that approx. 76% of Japanese DED patients are using artificial tears, and approx. 41% are using mucin secretagogues (partially in addition to artificial tears) [50]. With respect to market share in revenues, mucin secretagogues account for the biggest segment with approx. 64% in 2018, while artificial tears accounted for approx. 36% [50]. Corticosteroids presented again only a minor role in DED management in Japan, with a use in approx. 7% of DED patients and a market share of approx. 0.01% (Figure 5) [50].

5.3 Treatment guidelines

Besides the definition of DED in the different countries it is also important to analyze the different treatment guidelines of the medical communities in these 3 geographies.

5.3.1 USA

The Dry Eye Syndrome Preferred Practice Pattern® (PPP) has been issued by the American Academy™ of Ophthalmology. The current version is from 2018 and is summarized in the following.

5.3.1.1 Diagnosis

The PPP recommends that patients should have "*a comprehensive adult medical eye evaluation"* at a regular interval which should include the evaluation of tear film and ocular surface [23]. Additional evaluation may be considered including further DED relevant tests [23]. The evaluation should include an external examination as well as a slit-lamp biomicroscopy with the purpose to document the signs of DED, assess the quality, quantity, and stability of the tear film, and to determine other causes of ocular irritation [23].

The external examination should specifically focus on the skin (e.g., rosacea symptoms), the eye lids (e.g., incomplete blinking), the adnexa (e.g., enlargement of lacrimal glands), proptosis, cranial nerve function, and the hands (e.g., rheumatoid arthritis) [23].

The slit-lamp biomicroscopy evaluation should focus on the tear film (e.g., tear osmolarity, aqueous tear production (Schirmer's test ≤10 mm), TFBUT (< 10 sec), the eyelashes (e.g., trichiasis), the anterior and posterior eyelid margins (e.g., abnormalities of meibomian glands, or keratinization), and the puncta (e.g., presence and position of plugs) [23]. Additionally, it should investigate the conjunctiva, in particular the inferior fornix and tarsal conjunctiva (e.g., mucous threads, scarring, or keratinization), and the bulbar conjunctiva (all four quadrants) (e.g., punctate staining with rose bengal, lissamine green, or fluorescein dyes; hyperemia; keratinization) [23]. Finally, the slit lamp examination should also focus on the cornea (e.g., localized interpalpebral drying, punctate epithelial erosions assessed with fluorescein dye, punctate staining with rose bengal or fluorescein dyes, filaments, epithelial defects, thinning, ulceration, scarring, or neovascularization) [23].

The PPP recommends a detailed review of systems for any patient who has clinically significant DED [23]. However, diagnostic testing should be based on the review of systems and other clinical findings [23].

5.3.1.2 Treatment

The PPP guidance proposes a stepwise approach for the treatment of DED [23]. For mild DED patients should first be educated on factors supporting the disease, like cigarette smoking, antihistamine use, or long computer work or reading [23]. Modification of such factors is expected to already lead to an improvement [23]. Additionally, lid hygiene or warm compresses are recommended as well as the potential use of ocular lubricants, like artificial tears [23].

For moderate DED if above mentioned treatments are not effective, additional treatments are recommended like punctal occlusion or prescription drugs for anti-inflammatory therapy, with e.g., topical cyclosporine or lifitegrast, or topical corticosteroids for short-term duration [23].

For severe DED, if suggested treatments for mild and moderate DED are not adequate anymore, there is then the possibility to start treatments with e.g., oral secretagogues,

topical serum eye drops or topical corticosteroids for longer duration [23]. It is important that response to the treatment is assessed in follow-up evaluation to eventually adjust the treatment [23].

5.3.2 EU - exemplary Germany

Although drugs are partially centrally approved for all EU countries, medical treatment guidelines and reimbursement of therapies vary significantly between the European countries. Therefore, the guidance from Germany will be detailed here as an example of a major EU country.

The guideline for DED has been issued by the German Ophthalmology Society (DOG Deutsche Ophthalmologische Gesellschaft) and the Association of German Ophthalmologists (BVA Berufsverband der Augenärzte Deutschlands e.V.). The currently effective version is available in German and was published in 2019. A translated summary is provided in this section.

5.3.2.1 Diagnosis

The guidance states that a detailed examination is mandatory on the initial visit of the patient [22]. The examination should include medical history with complaints and risk factors, a visual acuity test, as well as an inspection of the ocular area [22]. Additionally, an examination of the ocular surface and the anterior segment of the eye with slit lamp and fluorescein staining is required [22]. Finally, all medical findings should be documented and discussed with the patient [22].

In the individual case additional examination might be required, like:

- Structured anamnesis with specific questionnaire
- Test of corneal sensitivity
- Staining of the ocular surface with additional dyes
- Schirmer test
- Interference imaging of the lipid layer
- Biochemical diagnostic of the tear film
- Meibography
- Impression cytology
- Microbiological or cytological swab

- Tear douche [22].

On follow up visits it is necessary to do an interim anamnesis, inspection, another examination with the slit lamp, as well as again document and discuss the findings [22].

5.3.2.2 Treatment

The treatment guidance is referencing on the DEWS II report which proposes a stepwise approach, similarly to the US DED PPP. In a first step drug free therapies should be considered, like correction of visual acuity, lid margin care, tear duct occlusion, or treatment of systemic causes [22].

If additional treatments are required, the following steps should be considered:

- Artificial tears, like surface active substances, mucin analogues, electrolyte substitutes, lipid containing artificial tears or semifluorinated alkanes
- Local immune modulation with steroids, cyclosporine A, lifitegrast (although not approved in the EU or Germany), Omega-3 fatty acids
- Serum eye drops
- Tear stimulation: local (Cyclosporine A) or systemic (pilocarpine analogue)
- Mucolytic agents
- Vitamin A acid 0.01% drops for keratinization of ocular surface epithelium [22].

The guidance also considers combination of the different treatments if necessary [22].

5.3.3 Japan

There is a treatment guidance available in Japan, but this is only available in Japanese language. Therefore, literature data, more precisely the *Consensus Report of the Asia Dry Eye Society* [24], will be detailed here to provide insight on the recommended Japanese DED diagnostics and treatments. As described in Section 3.2.1 the Japanese definition of DED is different to the US and EU definitions focussing more on a tear-film oriented therapy [24].

5.3.3.1 Diagnosis

Patients should have symptoms such as discomfort or visual disturbance to justify a careful evaluation of symptoms [24]. A number of widely accepted DED questionnaires are

regarded adequate tools, such as the OSDI, McMonnies questionnaire, Women's Health Study Questionnaire or the DED-related QOL score [24].

The definition of DED in Japan clearly focusses on the unstable tear film as a central issue of DED [24]. Therefore, measurement of the TFBUT using fluorescein dye is mandatory in DED diagnosis [24]. After dye instillation the subject should blink 3 times to ensure adequate mixing of the dye with the tears [24]. The time distance between last blink and the appearance of the first dark spot is measured [24]. It is recommended to always use the mean value of three measurements [24].

The Asia Dry Eye Society hereby defined a cut-off value of less than 5 seconds to diagnose DED [24]. TFBUT equal or greater than 5 seconds is not considered as DED [24]. Ocular surface damage and Schirmer's test are not regarded mandatory, even though they can be considered as they provide useful information especially for the diagnosis of aqueous-deficient DED and the evaluation of ocular damage which can lead to epithelial defects and inflammation [24].

The proposed diagnosis by the Asia Dry Eye Society specifically focusses on widely used clinical techniques to simplify disease diagnosis.

5.3.3.2 Treatment

Compared to the US and EU treatment guidance, the Japanese guidance proposes a different treatment strategy focusing on the tear film primarily v. A normal precorneal tear film is regarded as essential for a healthy ocular surface and an unstable tear film as the key risk factor for DED [24]. Therefore, the Asia Dry Eye Society has established the tear-film oriented therapy concept (Figure 6) [24].

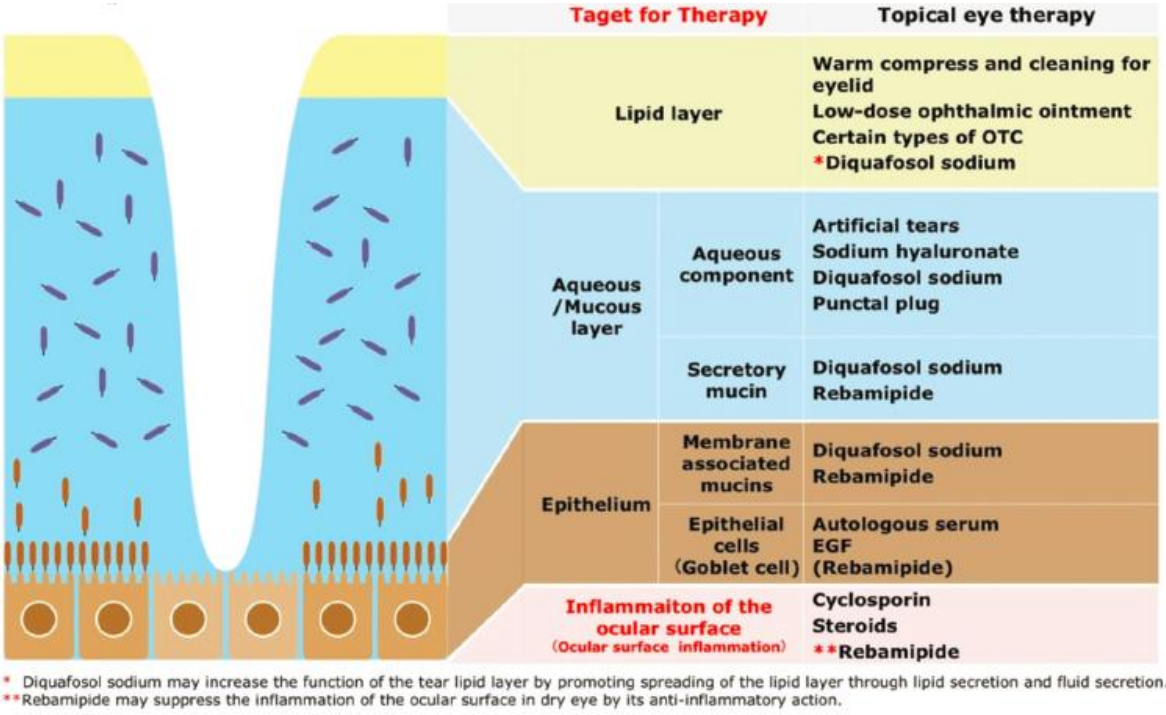

Figure 6: Concept of tear-film orientated diagnosis and therapy in Japan [24, 51]

This concept proposes that each layer of the tear film, i.e. the lipid layer, the aqueous component or the secretory mucin of the hydrated mucus layer, can become unstable and therefore lead to the development of DED [24]. With appropriate diagnostic tools, the layer which causes the disease can be determined, and a targeted treatment can be provided accordingly [24]. If for example the mucin layer is affected a mucin secretagogue may be prescribed [24]. If however, the lipid layer is unstable, lid hygiene and warm compresses should be the first treatment option [24]. Depending on disease severity, artificial tears or a mucin secretagogue like diquafosol might be additional therapeutic options [24].

Inflammation also plays a role in the Japanese treatment guidance, as it is expected that reduction of inflammation can improve all tear film layers by increasing both, mucin and aqueous secretion [24]. Anti-inflammatory drugs in Japan are also part of the daily DED treatment and are recognized as useful [24]. Nevertheless, the Asia Dry Eye Society Consensus Report makes it very clear that controlling inflammation is not regarded as the central strategy in DED treatment, but it is the production of a healthy stable tear film [24].

5.4 Regulatory guidelines for drug development

Until a few months ago, no regulatory guidelines were available for clinical development of drugs indicated to treat signs and symptoms of DED. The US FDA published a draft guideline

in December 2020. Pharmaceutical companies needed to consider Consensus Meetings or presentations from Agency representatives to develop their regulatory strategies.

In general, and in all regions, sponsors typically consult with regulatory agencies in scientific advice meetings, especially when no official guidance documents are available, to discuss the planned development program, to decrease the development risk and streamline activities.

5.4.1 USA

In December 2020, the US FDA published a draft Guidance for Industry on *Dry Eye: Developing Drugs for Treatment, giving considerations on several aspects like trial design, comparators, trial populations, safety and efficacy, clinical evaluations and pediatric development* [52]. The guidance focusses on the clinical development possibilities for new DED treatments and gives considerations on trial design, comparator selection, trial population, efficacy and safety, clinical evaluation, and pediatric development [52].

In terms of trial design, the draft guidance suggests that traditional environmental exposure trials but also challenge-model trials, like controlled chamber trials with regulated temperature, humidity etc., are acceptable [52]. The FDA recommends parallel, randomized, double masked clinical trials, which should show superiority over the control group [52]. The sponsor is free to also investigate the new drug as an add-on therapy [52]. Regarding the trial duration a wide range is acceptable, from 1-day trials in controlled environment up to 2 weeks or longer in natural exposure [52].

The guidance basically suggests using the investigational drug's vehicle as comparator [52]. Trials should be designed to demonstrate statistical and clinical superiority over the comparator treatment [52]. The guidance clearly states that equivalence or non-inferiority trials are not recommended, because there are currently no good assay validation methods available and DED trials have failed to demonstrate efficacy also for known effective therapies [52].

The following recommendations regarding trial population are given in the guidance:

- Inclusion of patients with ocular complaints consistent with DED symptoms. Inclusion criteria should include objective signs as well as subjective symptoms.

- Inclusion of relevant demographic subsets such as men and women, multiple ages, race/ethnicities, and eye color groups.
- Patients with DED secondary to scarring or destruction of conjunctival goblet cells, as well as patients with severe blepharitis or lid margin inflammation are regarded as specific patient population and separate indications, which should be studies separately from routine DED conditions [52].

The FDA generally expects that safety and efficacy are demonstrated in at least two independent trials, showing:

- a statistically significant difference between the investigational treatment and vehicle for at least one objective prespecified sign (including corneal staining, conjunctival staining, decreased tear breakup time, or decreased Schirmer's tear test score) and at least one subjective prespecified symptom (including blurred vision, light sensitivity, sandy or gritty feeling, ocular irritation, ocular pain or discomfort, and ocular itching), or
- a statistically significant difference between the percentage of patients achieving a complete resolution of corneal staining, or
- a statistically significant difference between the percentage of patients achieving a 10-millimeter increase or more in Schirmer's tear test scores [52].

A subjective symptom improvement can also be demonstrated by showing a statistically significant difference between the percentage of patients achieving a complete resolution of the symptom [52]. Efficacy for a sign and a symptom do not have to be demonstrated in the same clinical trial, but each may be demonstrated in more than one clinical trial [52]. The draft guidance also encourages the sponsors to actively discuss any scoring methods or scales used to measure efficacy variables with FDA before trial initiation [52].

Besides efficacy, another important issue of clinical trials is to demonstrate safety of the investigational treatment [52]. Therefore, the guidance recommends including sufficient patients to be able to identify drug-related adverse events that occur at a rate of 1% or greater, which should be at least 400 patients receiving the treatment at minimum market product concentration and frequency [52]. Before market application submission at least 300 patients need to have completed 6 weeks of follow-up after treatment start and at

least 100 patients should have completed 12 months follow up, respectively [52]. For reformulations of approved drugs safety information of 100 patients treated for at least 6 months is sufficient [52].

Clinical evaluations should be performed for each eye and at least include best corrected distance visual acuity at every visit, patient comfort examination before and after administration at every visit, a slit lamp examination of the anterior segment at baseline, mid trial, end of treatment, and two weeks after treatment discontinuation, as well as endothelial cell count, systemic clinical and laboratory evaluations and dilated fundus examinations at baseline and end of trial or at month 3 (whichever is later) [52].

Regarding pediatric development the FDA guidance states that sponsors should consider submitting waiver requests as DED is regarded occurring rarely in pediatric population [52].

5.4.2 EU

The EMA has currently no development guidance for DED products published but has reviewed several applications for drugs treating DED. A presentation of a member of the Swedish Medical Products Agency (MPA) from 2011 on *Dry Eyes Regulatory Perspectives* is available on the EMA website providing some impression on the European regulatory view [53]. The content of the presentation is summarized below:

One important aspect is the definition of the target population [53]. DED being a heterogenous disease requires the extraction of a clearly defined patient group which can benefit from the treatment, in terms of causes and history of DED, disease severity and duration [53]. Usually significant differences in both, signs and symptom endpoints are expected, however a significant effect in sign or symptom and a strong trend in the other might also be acceptable [53]. Regarding the selection of sign endpoints, the recommendation is to consider both, the target population, and the mechanism of action of the compound [53]. Typically, Corneal staining, Schirmer's test and TFBUT are established clinical endpoints [53].

For symptom endpoints a composite measure is recommended using a validated questionnaire [53]. The use of one single worst symptom evaluation is not recommended as changes in other parameters might not be directly linked to a worst symptom change [53]. Sponsors should focus on a relevant effect size rather than only statistical significance

and should include evaluation of clinically relevant mean changes and responder analyses [53]. In terms of comparator, using the vehicle is one option, alternatively the use of artificial tears as typical standard of care, if already used in the target population and vehicle composition is similar to the artificial tear [53]. Concomitant use of artificial tears is acceptable and might need to be considered to limit drop-out in the vehicle group [53].

Study duration is an important development criterion [53]. For efficacy of chronic DED treatments, primary evaluation is expected at 6 months to confirm that the effect is maintained over time [53]. For safety, 12 months data should be available according to ICH E1 [53]. Studies using controlled adverse environment (chamber studies) are considered useful in exploratory trials for the proof of concept and dose selection [53]. However, these studies are not regarded as adequate pivotal trials that require environmental studies [53]. The key concerns are that the selected population might not be representative for the target population and that there might be an overestimation of effect due to real life heterogeneity [53].

For anti-inflammatory products special development considerations are required as the inflammation is expected to be a secondary manifestation, which might need to be addressed with biomarkers [53]. In general, superiority trials are not recommended due to the lack of EU comparators as well as assay sensitivity [53]. Additionally, as historically many DED studies failed to confirm previous results, two independent confirmatory trials are recommended [53].

Due to the lack of a formal guidance for development, potential regulatory expectations for existing or future DED drugs are evaluated based on available marketing authorization information or information on refusal of marketing authorizations in Section 6.

5.4.3 Japan

As in the EU, there is no official development guidance from the PMDA available for Japan. Therefore, potential opinions or expectations on DED drug developments for the Japanese market will be shown from available marketing authorization information and literature in Section 6.

6 Approved Dry Eye Drugs

The currently approved DED drugs in the respective markets will be detailed (ordered by approval date), focusing on the target indication, available information on the clinical data package and potential reasons for withdrawal of application for marketing authorization.

6.1 Hyalein

Hyalein® is a 0.1% sodium hyaluronate ophthalmic solution for topical use as eye drop by Santen [54]. The product was approved in Japan in 1995 and is formally the first DED drug worldwide [55]. Hyalein is also available in other Asian countries, like China, Singapore or Korea, partially under the name Hyalid® or Sanlein® [55]. According to its label Hyalein is indicated for "*Keratoconjunctival epithelial disorder resulting from the following diseases: Intrinsic diseases such as Sjögren's syndrome, Stevens-Johnson syndrome and sicca syndrome (dry eye) or Extrinsic diseases caused by surgery, drugs, trauma, contact lens wearing, etc"* [54]. Hyalein needs to be instilled with one drop in each affected eye, 5-6 times daily [54].

There is no explicit information on the clinical development program of Hyalein available. A summary of observations in clinical trials of Hyalein is available in literature and outlined in the following. Compared with placebo (artificial tear base), Hyalein was significantly more effective in treating patients with keratoconjunctival epithelial disorder associated with DED [55]. Foreign body sensation score was reduced significantly more with Hyalein than with placebo after 2 and 4 weeks of treatment [55]. Furthermore, the fluorescein staining score was rated as improved or better in more eyes treated with Hyalein than with placebo [55].

As sodium hyaluronate eye drops are available as medical devices in the EU and OTC drugs in the USA, Hyalein is not expected to be submitted for a marketing authorization in those countries.

6.2 Restasis

Restasis® is a 0.05% cyclosporine ophthalmic emulsion for topical use as eye drop developed by Allergan [56]. Cyclosporine is a calcineurin inhibitor immunosuppressant which inhibits the production of cytokines involved in the regulation of T-cell activation and

therefore provides anti-inflammatory effects [57]. The product is approved in the US since 2003 and available in other selected countries (e.g., India, China, Australia). According to the label Restasis is indicated to "*increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca"* [56].

The initial New Drug Application of Restasis was denied by US FDA after an advisory panel expressed doubts about its efficacy (complete response letter 2000) [58]. An additional subgroup analysis together with the demonstration that 10 mm change in Schirmer's test is regarded clinically relevant were included in a resubmission which finally resulted in US product approval in 2003 [58].

The complete clinical development program submitted in the NDA consisted of three multicenter, randomized, and vehicle-controlled clinical studies treating approx. 1,200 patients with DED (Table 1) [58]. Restasis demonstrated a statistically significant increase in Schirmer wetting of 10 mm versus vehicle at six months in patients whose tear production was suppressed due to ocular inflammation [56, 58, 59]. The increase in Schirmer wetting of >10 mm is perceived by FDA as an improvement of a clinical sign with a positive impact on symptoms as patients with Schirmer >10 mm not being classified as dry eye patients (see section 3.2.3) [58].

Table 1: Clinical regulatory Phase 3 program of Restasis [58, 59]

Trial number	**Treatment**	**Study duration**	**Endpoints (results in italic for 0.05%)**
192371-002	1 drop per eye twice daily with Cyclosporine 0.05% / Cyclosporine 0.1% / Vehicle	6 months	**Primary:** Sum of Corneal Fluorescein and Interpalpebral conjunctival lissamine green score staining *Significant difference / MET* OSDI score *No significant difference / NOT MET* **Secondary (selected):** Schirmer's test score *No significant difference* Symptoms of DED *No significant difference*
192371-003	1 drop per eye twice daily with Cyclosporine 0.05% /	6 months	**Primary:** Sum of Corneal Fluorescein and Interpalpebral conjunctival lissamine green score staining

Trial number	Treatment	Study duration	Endpoints (results in italic for 0.05%)
	Cyclosporine 0.1% / Vehicle		*No significant difference / NOT MET* OSDI score *No significant difference / NOT MET* **Secondary (selected):** Schirmer's test score *Significant difference* Symptoms of DED *No significant difference*
192371-501	1 drop per eye twice daily with Cyclosporine 0.05% / Cyclosporine 0.1% / Vehicle	12 weeks	**Primary:** Corneal Fluorescein staining *Significant difference / MET* OSDI score *No significant difference / NOT MET* **Secondary (selected):** Schirmer's test score *No significant difference* Symptoms of DED *No significant difference*

Allergan also attempted to bring Restasis (planned EU product name: Restaysis) three times to the EU market: in 1999, 2008 and 2018 [60]. In all cases Allergan had to withdraw the application for marketing authorization after negative feedback from the EMA [60]. The EMA did not follow Allergan's argumentation that 10 mm change in Schirmer's test was shown to be clinically relevant [60]. The detailed EMA withdrawal report is publicly available for the third procedure only. For the first two reviews of the Restasis dataset by the EMA the applications were withdrawn prior to conclusion of the respective procedures due to concerns over inadequate demonstration of efficacy with the presented clinical data [60].

In 2018, Allergan re-submitted a marketing authorization application with an additional retrospective analysis of the existing data but did not conduct additional clinical studies [60]. During the review, the EMA raised a number of concerns, which finally led to the third withdrawal of the marketing application: EMA was concerned that (1) the retrospective analysis was data-driven and may have been biased in favor of the study drug and (2) the analysis did not invalidate the concerns on observed inconsistencies in the pivotal trials with regards to outcomes, trials, patient populations and dose response [60].

It is not known whether Restasis has been submitted for a marketing authorization in Japan yet.

6.3 Diquas

Diquas® is a 3% diquafosol sodium ophthalmic solution for topical use as eye drop by Santen. Diquafosol is a P2Y2 receptor agonist that promotes tear fluid and mucin secretion [61]. The product was approved in Japan in 2010 [62]. Diquas is indicated for the "*Treatment of Dry eye and should be used in patients diagnosed with dry eye, associated with keratoconjunctival epithelium disorders that accompany lacrimal fluid abnormality"* [61]. Diquas needs to be instilled with one drop in each affected eye, 6 times daily [61].

The clinical development program consisted of several multicenter, randomized, and controlled clinical studies with DED patients (main studies summarized in Table 2) [62]. The completed trials could demonstrate that diquafosol significantly decreased fluorescein corneal staining and Rose-Bengal staining scores compared with sodium hyaluronate artificial tears at Week 4 and also improved TFBUT [62]. Long-term treatment for six months significantly improved both subjective (dry eye symptom score) and objective signs (ocular staining score and tear function tests) [62].

Table 2: Clinical regulatory program of Diquas [62, Clinicaltrials.gov]

Trial number	**Treatment**	**Study duration**	**Endpoints (results in italic)**
00890404 (NCT # NCT01189032)	1 drop six times daily with Diquafosol 1% / Diquafosol 3% / Sodium hyaluronate 0.1%	6 weeks	**Primary**: Corneal fluorescein staining score *Significant difference / MET* **Secondary:** Corneal rose bengal staining score *Significant difference* Tear film break up time *No significant difference* Dry Eye Symptom Score *Significant difference*
00890602 (NCT # NCT01240382)	1 drop six times daily with Diquafosol 3% / Sodium hyaluronate 0.1%	4 weeks	**Primary**: Corneal fluorescein staining score *No significant difference; non-inferiority met* Corneal rose bengal staining score *Significant difference / MET* **Secondary:** Tear film break up time *No significant difference*

Trial number	Treatment	Study duration	Endpoints (results in italic)
			Dry Eye Symptom Score *Significant difference*

Diquafosol was initially developed by Inspire Pharmaceuticals for the US market. A New Drug Application (NDA) including a full data set with US clinical trials (NCT00037661, NCT00403715, NCT00404131, NCT00679718, NCT00680108) was submitted to the FDA in 2003 [9]. FDA had concerns in relation to efficacy demonstration in both, signs and symptoms, which posed difficulty for secretagogue product candidates [9]. The company's final effort to win regulatory approval for diquafosol failed in 2010 [9]. Santen then conducted separate trials (shown in Table 2) in Japanese population and successfully brought the product to the Japanese market. It is not known whether Diquas was ever submitted for a marketing authorization in the EU.

6.4 Mucosta

Mucosta® is a 2% rebamipide ophthalmic suspension for topical use as eye drop by Otsuka Pharmaceuticals [63]. Rebamipide is a quinolinone derivative which increases the secretion of both membrane-associated and secreted-type mucins through mucin production in the conjunctival goblet cells, and in the corneal epithelial cells [62]. The product is currently approved in Japan since 2012 [62]. According to the label Mucosta "*enhances the production of mucin, a component of tears, to stabilize tear film and thereby improve corneal epithelium damage. It is usually used to treat dry eye"* [63]. Mucosta needs to be instilled with one drop in each affected eye, four times daily [63].

The clinical development program consisted of several multicenter, randomized, and controlled clinical studies with DED patients (main studies summarized in Table 3) [62, 64, 65]. The conducted trials could show that rebamipide significantly improved subjective symptoms, such as foreign body sensation, dryness, photophobia, eye pain, and blurred vision as well as patients' overall impressions, and also improved fluorescein corneal staining scores [62]. Rebamipide was significantly more effective against objective signs and subjective symptoms than 0.1% sodium hyaluronate in the treatment of DED [62].

Table 3: Clinical regulatory program of Mucosta [64, 65]

Trial number	Treatment	Study duration	Endpoints (results in italic)
Phase-2 trial (NCT # 00475319)	1 drop per eye four times daily with Rebamipide 1% / Rebamipide 2% / Placebo	4 Weeks	**Primary**: Corneal fluorescein staining score *Significant difference / MET* **Secondary:** Conjunctival lissamine green staining score *Significant difference* Tear film break up time *Significant difference* Schirmer's test score *No significant difference* Dry Eye Symptoms *Significant difference*
Phase-3 trial (NCT # 00885079)	1 drop per eye four times daily with Rebamipide 2% / 1 drop six times daily with Sodium hyaluronate 0.1%	4 Weeks	**Primary**: Corneal fluorescein staining score *Significant difference + non-inferiority met* Conjunctival lissamine green staining score *Significant difference / MET* **Secondary:** Tear film break up time *No significant difference* Schirmer's test score *No significant difference* Dry Eye Symptoms *Significant difference (foreign body sensation)*

Novartis licensed rebamipide from Otsuka in 2005 but terminated the project in 2008 [9]. Otsuka and Acucela Inc. then announced a co-development agreement with Acucela leading the regulatory process at FDA, which ended in failure in 2013 [9]. It is not known whether Mucosta was submitted for a marketing authorization in the EU yet.

6.5 Ikervis

Ikervis® is a 0.1% cyclosporine ophthalmic emulsion for topical use as eye drop by Santen [66]. The product is currently approved in the EU since 2015 [66]. Ikervis is indicated for the "*Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes"* [66]. It needs to be instilled with one drop in each affected eye, once daily at bedtime [66].

The clinical development program to demonstrate efficacy for EU approval consisted of two pivotal multicenter, randomized, and vehicle-controlled clinical studies treated approx. 741 patients with DED (Table 4) [67]. The conducted trials could formally not show consistent superiority primary endpoints (corneal fluorescein staining score in SICCANOVE and SANSIKA trials); the drug was finally approved on a secondary sign endpoint by showing a statistically significant reduction in corneal fluorescein staining versus its vehicle [67]. As no significant improvement in symptoms could be demonstrated but the improvement in corneal staining was assessed as clinically relevant, the indication was restricted to a "severe keratitis treatment" instead of a broader DED population [67].

Table 4: Clinical regulatory Phase 3 program of Ikervis [67]

Trial number	**Treatment**	**Study duration**	**Endpoints (results in italic)**
NVG06C103 (EudraCT # 2007-000029-23) SICCANOVE	1 drop daily with Cyclosporine 0.1% / Vehicle	6 months	**Primary**: Corneal fluorescein staining score *Significant difference / MET* Visual Analogue Scale score *No significant difference / NOT MET* **Secondary:** Conjunctiva Lissamine green staining score *Significant difference* Ocular discomfort symptoms *No significant difference*
NVG10E117 (EudraCT # 2011-000160-97) SANSIKA	1 drop daily with Cyclosporine 0.1% / Vehicle	6 months	**Primary**: Corneal Fluorescein Staining-OSDI responder rate *No significant difference / NOT MET* **Secondary:** Corneal fluorescein staining score *Significant difference* Visual Analogue Scale score *No significant difference* OSDI Score *No significant difference*

It is not known whether Ikervis was submitted for a marketing authorization in the US or Japan yet.

6.6 Xiidra

Xiidra® is a 5% lifitegrast ophthalmic solution for topical use as eye drop owned by Novartis [68]. The product was approved in the US in 2016 and is the second US DED drug after

Restasis was approved in 2002 [68]. Lifitegrast is an LFA-1 antagonist which prevents the adhesion, activation, migration, and proliferation of lymphocytes, which ultimately lead to cytokine secretion, cell destruction, and self-amplification of the inflammatory immune response that further aggravates symptoms of DED [69]. According to the label, Xiidra is indicated *"for the treatment of the signs and symptoms of dry eye disease (DED)"* [68]. Xiidra needs to be instilled with one drop twice daily (approximately 12 hours apart) into each eye [68].

Xiidra was initially developed by Sarcode and later by Shire, the latter submitted the NDA to the US FDA initially without the third Phase-3 trial OPUS-3 (Table 5) [70]. In a first response, FDA did not approve the drug, sending a Complete Response Letter including the request for an additional clinical trial (OPUS-3) to provide substantial evidence of efficacy in the intended patient population [70].

With the resubmission of the extended clinical development program consisting of four multicenter, randomized, and vehicle-controlled clinical studies in 1,181 patients with DED (Table 5), the drug was the first drug in the US approved for the treatment of the signs and symptoms of DED [70]. Xiidra demonstrated efficacy by significant reduction of the inferior fluorescein corneal staining score at Day 84 compared to its vehicle, and also reduced the patient's eye dryness score (using VAS) at visits on Day 42 and Day 84 [68, 70].

Table 5: Clinical regulatory program of Xiidra [70]

Trial number	**Treatment**	**Study duration**	**Endpoints (results in italic)**
1118-KCS-100 (NCT # 00926185) Controlled Adverse Environment Study	1 drop per eye twice daily with Lifitegrast 0.1% / Lifitegrast 1% / Lifitegrast 5% / Vehicle	12 weeks	**Primary**: Inferior fluorescein corneal staining score at Day 84 *No significant difference / NOT MET* **Secondary** (selected): Visual-Related Subscale of the Symptom Functional Scale Score at Day 84 *Significant difference*
1118-KCS-200 OPUS-1 (NCT # 01421498)	1 drop per eye twice daily with Lifitegrast 5% / Vehicle	12 weeks	**Co-Primary**: *NOT MET* Inferior fluorescein corneal staining score at Day 84 *Significant difference* Visual-Related Subscale of the Symptom Functional Scale Score at Day 84

Trial number	Treatment	Study duration	Endpoints (results in italic)
			No significant difference
1118-DRY-300 OPUS-2 (NCT # 01743729)	1 drop per eye twice daily with Lifitegrast 5% / Vehicle	12 weeks	**Co-Primary**: *NOT MET* Inferior fluorescein corneal staining score at Day 84 *No significant difference* Eye dryness Score (VAS) at Day 84 *Significant difference*
SHP606-304 OPUS-3 (NCT # 02284516)	1 drop per eye twice daily with Lifitegrast 5% / Vehicle	12 weeks	**Primary**: Eye Dryness Score at Day 84 *Significant difference / MET* **Secondary** (selected): Eye Dryness Score at Day 42 *Significant difference* Eye Dryness Score at Day 14 *Significant difference*

After US approval Novartis submitted the FDA data package to the EMA for marketing authorization application in the EU [71]. However, the EMA raised efficacy concerns during their review and Novartis then withdrew the application [71]. Major objections were that all OPUS studies failed to demonstrate a convincing effect on signs related to DED and that the relevance of effect on the Eye Dryness Score would be questionable, especially with regards to inconsistencies of symptom results across all trials [71]. As all pivotal trials had a duration of 12 weeks long-term efficacy data were lacking in view of EMA which is regarded as a major concern as DED is perceived as a chronic disease [71]. The EMA finally concluded the assessment with a negative benefit-risk ratio [71].

It is not known whether Xiidra was submitted for a marketing authorization in Japan yet.

6.7 Cequa

Cequa™ is a 0.09% cyclosporine ophthalmic solution for topical use as eye drop by Sun Pharma [72]. The API cyclosporine as treatment for DED is already known from Restasis. The product is currently approved in the US since 2018 [72]. According to its label, Cequa is indicated to *"increase tear production in patients with keratoconjunctivitis sicca (dry eye)"* [72]. Cequa needs to be instilled with one drop twice daily (approximately 12 hours apart) into each eye [72].

The clinical development program which presented the basis for US approval consisted of two pivotal, multicenter, randomized, adequate and well-controlled CAE clinical studies

treated 1,048 patients with DED (Table 6) [73]. The drug was approved on a statistically significant ($p<0.01$) sign endpoint compared to vehicle at Day 84 [72]. An increase of ≥10mm from baseline in Schirmer's test was seen in approx. 17% of Cequa-treated patients compared to approx. 9% of vehicle-treated patients [72, 73].

Table 6: Clinical regulatory program of Cequa [73]

Trial number	**Treatment**	**Study duration**	**Endpoints (results in italic)**
OTX-101-2014-001 (NCT # 02254265)	1 drop per eye twice daily with Cyclosporine 0.05% / Cyclosporine 0.09% / Vehicle	12 weeks	**Co-Primary**: Total conjunctival staining score at Day 84 *Significant difference / MET* Global symptom score (SANDE) at Day 84 *No significant difference / NOT MET* **Secondary** (selected): Tear film break up time at Day 84 *No significant difference* Total corneal fluorescein staining score at Day 84 *No significant difference* Schirmer's test score at Day 84 (post-hoc responder analysis on FDA request) *Significant difference*
OTX-101-2016-001 (NCT # 02688556)	1 drop per eye twice daily with Cyclosporine 0.09% / Vehicle	12 weeks	**Primary**: Schirmer's test score at Day 84 (% of eyes ≥10mm increase) *Significant difference / MET* **Secondary** (selected): Central corneal fluorescein staining score at Day 84 *No significant difference* Global symptom score (SANDE) at Day 84 *No significant difference*

The approval of Cequa followed the regulatory path Restasis had established with the US FDA. It was the second drug that successfully followed this path. It is not known whether Cequa was submitted for a marketing authorization in the EU or Japan yet.

6.8 Eysuvis

Eysuvis™ is a 0.25% loteprednol etabonate ophthalmic suspension for topical use as eye drop by Kala Pharmaceuticals [74]. Loteprednol etabonate is a corticosteroid already used

in ophthalmology which inhibits prostaglandin production and therefore inhibits the inflammatory response to a variety of inciting agents and delay or slow healing [74]. The product is currently approved in the US since 2020 [74]. According to the label Eysuvis is indicated "*for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease"* [74]. Eysuvis needs to be instilled with two drops four times daily into each eye [74].

The clinical development program which presented the basis for US approval consisted of four, multicenter, randomized, and controlled clinical studies treated approx. 2900 patients with DED (Table 7) [74]. The drug was approved on a sign as well as a symptom endpoint [74]. Eysuvis significantly reduced conjunctival hyperemia at Day 15 compared to vehicle, and also reduced the patient's Ocular Discomfort Severity (using VAS) at Day 15 [74]. The usage is limited to 2 weeks due to potential long-term risk of corticosteroid [74].

Table 7: Clinical regulatory program of Eysuvis [75, 76, 77, Clinicaltrials.gov]

Trial number	**Treatment**	**Study duration**	**Endpoints (results in italic)**
KPI-121-C-002 (NCT # 02188160) Phase-2	1-2 drop per eye four times daily with Loteprednol 0.25% / Vehicle	28 days	**Primary**: Bulbar Conjunctival Hyperemia *Significant difference / MET* Ocular Discomfort Severity *No significant difference / NOT MET*
KPI-121-C-006 (NCT # 02813265) STRIDE-1	1-2 drop per eye four times daily with Loteprednol 0.25% / Vehicle	14 days	**Primary**: Ocular Discomfort Severity *Significant difference / MET* Conjunctival Hyperemia *Significant difference / MET* **Secondary** (selected): Corneal fluorescein staining score *No significant difference*
KPI-121-C-007 (NCT # 02819284) STRIDE-2	1-2 drop per eye four times daily with Loteprednol 0.25% / Vehicle	14 days	**Primary**: Conjunctival Hyperemia *Significant difference / MET* Ocular Discomfort Severity *No significant difference / NOT MET* **Secondary** (selected): Corneal fluorescein staining score *Significant difference*
KPI-121-C-011 (NCT # 03616899) STRIDE-3	1-2 drops per eye four times daily with Loteprednol 0.25% / Vehicle	14 days	**Primary**: Ocular Discomfort Severity Day 15 *Significant difference / MET* **Secondary** (selected): Conjunctival Hyperemia *Significant difference*

Trial number	Treatment	Study duration	Endpoints (results in italic)
			Corneal fluorescein staining score *Significant difference*

It is not known whether Eysuvis was submitted for a marketing authorization in the EU or Japan yet.

7 Current developments

The DED drug market is expected to significantly grow in the coming years with estimated global sales of over 10 billion USD due to a significant unmet medical need in this space [50]. There are several development projects underway which are expected to apply for marketing authorizations in key geographies [50].

Global development efforts primarily focus on the US market with more than 10 products being in late-stage clinical trials in the US [50]. The products partially rely on known APIs and mechanisms, like cyclosporine, but there are also NCEs with new mode-of-actions (MOAs) investigated to treat DED. An overview of current late-stage US developments is shown in Table 8 [50].

All listed projects have US investigator sites only listed in the clinicaltrials.gov register. There is currently no DED development program with multi-national clinical trials known. Instead, companies seem to prioritize US approval. The ongoing clinical trials use the previously established endpoints for DED which are accepted by the regulatory authorities and have shown to be relatively reproducible in the past (see Table 8). The historic failure rate in clinical trials for DED has nevertheless been quite high and above average for clinical trials based on their development stage, resulting in several discontinued projects [78, 79].

Table 8: Overview of current DED drug developments in the US [50]

Product	Company	API class	Trial endpoints	Expected market entry
OC-01 Nasal spray	Oyster Point	Nicotinic acetylcholine receptor agonist	Schirmer's test	2021
Tavilermide	Mimetogen	Neurotrophic tyrosine kinase receptor agonist	Eye dryness score, Total corneal fluorescein staining	2022

Product	Company	API class	Trial endpoints	Expected market entry
RGN-259	RegeneRx	Thymosin beta 4 based peptide	Corneal staining, Ocular discomfort	2022
CyclASol	Novaliq	Cyclosporine	Total corneal fluorescein staining, Ocular surface disease index	2023
NOV03	Bausch +Lomb	Semifluorinated alkane, Lipid layer stabilization	Total corneal fluorescein staining, Visual Analogue Scale	2023
Voclosporin	Aurinia	Cyclosporine Analogue	Increase in Schirmer's Test	2023
Tanfanercept	HanAll	Tumor necrosis factor inhibitor	Inferior corneal and conjunctival staining scale, Ocular discomfort scale	2023
Tivanisiran	Sylentis	Small interfering RNA	Visual Analogue Scale, Corneal fluorescein staining, Conjunctival hyperaemia scores	2023
Visomitin	Mitotech	Antioxidant	Ocular discomfort score, Conjunctival fluorescein staining	2023
Reproxalap	Aldeyra	RASP (reactive aldehyde species) Inhibitor	Ocular dryness, Fluorescein nasal region score	2023
SJP-0035	Senju	Peroxisome proliferator-activated receptor delta agonist	Corneal fluorescein staining	Status unknown

In the EU Clinical Trials Register as well as in the Japanese NIPH Clinical Trials Search there are currently only a few ongoing and new dry eye development studies listed. In Japan, additional studies with diquafosol formulations from Santen are listed, as well as a study with SJP-0132 from Senju. There is no further information on SJP-0132 available. In Europe, studies for two cyclosporine formulations are listed, but the current status of development is unknown.

8 Discussion and Conclusions

8.1 Comparison of disease definition and treatment

DED is a common global disease with a prevalence higher than other major ophthalmic indications like for example glaucoma [9]. Symptomatology is a key driver of this ocular

surface disease which also is a major challenge to adequately define and characterize it [21]. Certain efforts have been made to develop a common understanding and a global consent of the disease by international initiatives like the TFOS DEWS I and II. But disease definitions still differ across different geographies. Table 9 gives an overview of the different definitions, treatment recommendations and types of available prescription drugs in the US, the EU and Japan. In the USA and the EU there is a distinct focus on inflammation when defining DED [22, 23]. The US definition highlights *'… associated with inflammatory disease of the ocular surface…*' [23] and the EU definition, which is identical to the DEWS II definition, states '… *accompanied by ocular surface inflammation…*' [translated from 22]. The focus on inflammation in the definition might also be based on the historical evolution of the disease management as in the USA and in the EU only drugs focussing on inflammation management are approved for the treatment of DED. The currently approved drugs for the treatment of DED with an anti-inflammatory mode of action are using non-glucocorticoid immunomodulators, LFA-1 antagonists, and corticosteroids as active ingredients (see section 6).

Conversely, in Japan, besides the artificial tear Hyalein approved back in the 1990s, two secretagogues are approved as drugs for DED treatment, which promote mucin production and restorage of the tear film. Here, the therapeutic focus appears to be more on the tear film itself [24]. This is reflected in both, the disease definition as well as the disease management. The definition of DED in Japan does not even mention inflammation as part of the disease description [24]. It rather focusses on *'… characterized by unstable tear film…*' [24]. However, such a conclusion must be seen in relative terms, as the further explanation shows that the Japanese understanding of the disease also considers inflammation as a possible consequence of DED that depending on its severity still can be a focus of treatment [24]. Therefore, it can be concluded that inflammation likely plays a key role in DED etiology but there remains significant uncertainty about its importance to improve the disease in the long run.

Table 9: Overview of DED definitions and treatment in the USA, the EU and Japan

	USA	**EU**	**Japan**
Organizations	TFOS DEWS AAO	TFOS DEWS BVA / DOG	TFOS DEWS Asian Dry Eye Society

	USA	**EU**	**Japan**
Definition	*'group of disorders of the tear film that are due to reduced tear production or tear film instability, associated with ocular discomfort and/or visual symptoms and inflammatory disease of the ocular surface' [23]*	*'multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles' [22]*	*'multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage' [24]*
Main focus	Inflammation	Inflammation	Tear film instability
Treatment approach	Stepwise *[23]*	Stepwise *[22]*	Stepwise *[24]*
Suggested therapies	- Education with potential change of local environment, habits, diet - Lid hygiene/ compresses - Artificial tears - Topical prescription drugs *[23]*	- Education with potential change of local environment, habits, diet - Correction of visual acuity - Lid hygiene/ compresses - Artificial tears - Topical prescription drugs - Systemic anti-inflammatory therapy *[22]*	- Lid hygiene/ compresses - Artificial tears - Topical prescription drugs *[24]*
Available topical drugs	- Non-glucocorticoid immunomodulator - LFA-1 antagonist - Corticosteroid - Secretagogues	- Non-glucocorticoid immunomodulator - Corticosteroid (for ocular inflammation)	- Secretagogues - Corticosteroid (for ocular inflammation) - Sodium hyaluronate

Besides all the differences in the various definitions and specifically the role and importance of inflammation as a result of DED and its value for the treatment, all treatment guidelines propose a stepwise treatment approach [22, 23, 24]. Before recommending prescription drugs, patients should always be educated on the disease and potential risk factors to eventually change certain behaviors or dietary components thereby decreasing risks and subsequently potentially reduce DED symptoms [22, 23, 24]. Another common point is proposing lid hygiene and warm compresses, which could especially be beneficial

in patients with a meibomian gland component, as this can help reduce microbial growth and increase fluidity of the meibum [22, 23, 24]. A subsequent step is then the use of ocular lubricants or artificial tears which is acknowledged to be effective in the treatment of milder forms of DED [22, 23, 24]. In all guidelines, topical prescription drugs are only recommended in a later treatment step to treat rather severe DED patients having a persistent DED condition that could not be adequately treated with the afore mentioned therapies [22, 23, 24].

Regarding diagnostic tools and outcome measures, the proposed tests are very similar in the different countries, although the cut-off levels for disease indication for some tests may vary. For example, TFBUT is regarded abnormal if ≤ 10 sec in the US and the EU, whereas Japan suggests a more severe cut-off value of ≤ 5 sec [22, 23, 24]. Similarly, for Schirmer's tear secretion test a cut-off value of < 10 mm is regarded abnormal in the USA and the EU, and Japan again is proposing a lower, more severe value of ≤ 5 mm (see also Table 10) [22, 23, 24].

What remains not fully clear is which tests are the essential/best ones to diagnosing DED. It further needs to be considered that not all ophthalmologists might be able to perform all of the tests in daily practice. It is widely accepted that DED is highly variable and therefore tests might vary in their importance depending on the individual patient [21]. Thus, this additionally complicates consistent disease diagnosis and appropriate treatment selection. However, it can be noted that as a typical base set of diagnostics the following techniques seem to be widely established: symptom questionnaire, slit lamp examination including dye to examine cornea and conjunctiva, and TFBUT [31].

For the clinical development of drug therapies, the selected sign endpoints used in the trials are usually similar with being mainly corneal or conjunctival staining (although using different scales), Schirmer's test, and symptom questionnaires [78]. For symptom questionnaires there seems to be a trend from overall symptom questionnaires, like the OSDI© which often failed in clinical trials, to VAS discomfort or dryness questionnaires which focus more on specific symptoms (see section 6). For the listed endpoints, experience from previous trials with regulatory acceptance is available, which helps the developing companies to define their regulatory strategy and decrease development risk. The history of high probability of trial failure suggests that next to endpoints the variability

of the diagnostics methods may have an impact too (see section 8.2) [79]. Companies coped with this observation by including new diagnostic tools in their clinical development, primarily as secondary or exploratory endpoints [48]. This strategy may help to better understand the disease and to identify more robust endpoints which better correlate with the disease severity and can consistently display treatment effects.

8.2 Comparison of regulatory expectations

The requirements of the respective regulatory agencies for clinical data of potential new drugs are of utmost importance for pharmaceutical companies. The regulatory requirements are summarized in Table 10. Differences in regulatory requirements are evident. For example, the trial duration expectations significantly vary, with the US FDA accepting trial data with 14 days treatment duration or even 1-day data from controlled adverse environment studies, the Japanese PMDA expects at least 1-month data and the European EMA even 6-month data as they argue DED being a chronic disease [6, 52, 53].

Controlled environment studies are discussed quite controversial. The fact that all patients are expected being normalized to a similar level is often regarded as beneficial. Critics argue the model is also regarded as artificial and not considering relevant aspects of a natural environmental exposure [53]. Therefore, several countries, including the EU and Japan, are not accepting controlled-adverse environment studies as pivotal trials.

Table 10: Overview or regulatory expectations for DED drugs in the USA, the EU and Japan

	USA (FDA)	**EU (EMA)**	**Japan (PMDA)**
Minimum trial duration	Controlled adverse environment: 1 day Natural exposure: 14 days [52]	Natural exposure: 6 months [53]	Natural exposure: 1 month [6]
Trial type	Superiority [52]	Superiority [53]	Superiority Non-inferiority over approved drugs [6]
Controlled adverse environment studies	Acceptable [52]	Not acceptable for pivotal trials [53]	Not acceptable for pivotal trials [6]
Endpoints	Sign: *Unspecified* Symptom: *Unspecified* [52]	Sign: *Unspecified* Symptom: *Unspecified* [53]	Sign: *Corneal Fluorescein Staining* Symptom: *Unspecified* [6]
Number of pivotal trials	Significance in both sign and symptom in	Two independent trials, however significance in sign	Significance in two independent trials [6]

	USA (FDA)	EU (EMA)	Japan (PMDA)
	two independent trials [52]	with trend in symptom in one trial and significance in symptom with trend in sign in second trial may be acceptable [53]	
Recommended Control	Vehicle [52]	Vehicle [53]	Vehicle Approved drug [6]

Generally, efficacy trials demonstrating API superiority over vehicle are expected, although Japan also considers non-inferiority studies over approved drugs (mainly Hyalein) [6, 52, 53]. Typically, one sign and one symptom endpoint is expected to show significant improvement during therapy, and to be confirmed in two independent trials to ensure consistency [6, 52, 53]. However, in the EU, significance in the sign endpoint with a trend in the symptom endpoint in one trial together with a second trial showing significance in the symptom endpoint with a trend in the sign endpoint may be sufficient [53].

All regulatory authorities recommend the use of vehicle as control in the clinical trials, which corresponds to the US and EU trials of the last 20 years [6, 52, 53]. It should be noted that the vehicles are often very similar to available artificial tears, which are also recommended for certain DED therapies. It is therefore not surprising that vehicle effects are very common in DED trials, which means that the treatment with vehicle alone may already improve various signs and symptoms of DED [47]. This leads to the effect that demonstration of superiority of a new drug is challenging and that the treatment effect of the drug needs be sufficiently large for achieving a statistically significant difference between drug and vehicle treatment [47]. Superiority trials versus an approved therapy like for glaucoma are not established or even recommended by regulators due to the lack of appropriate comparators as mode of action and efficacies of approved drugs may vary significantly in different patient groups [47, 52, 53].

The comparison of the currently approved drugs for treating DED demonstrated that indications of the products vary substantially (Table 11). While some products, e.g., the newer ones like Xiidra or Eysuvis, are indicated for the treatment of both, the signs and the symptoms of DED, other products are indicated for more specific effects or aspects of the DED therapy [68, 74]. Restasis and Cequa are typical examples as they are indicated to induce tear production [56, 72]. Considering the annual sales of Restasis, it is very likely

that the product is not only prescribed for this restricted patient population, but rather generally used for the treatment of DED [9].

Table 11: Comparison of approved DED drugs (order by market)

	Indication	**Trial duration**	**Control**	**Approved Endpoint**	**Number of pivotal trials**
Restasis (US)	Increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with DED	6 months	Vehicle	Schirmer's test score	3
Cequa (US)	Increase tear production in patients with DED	12 weeks	Vehicle	Schirmer's test score	2
Xiidra (US)	Treatment of the signs and symptoms of DED	12 weeks	Vehicle	Inferior fluorescein corneal staining score D84 Eye dryness Score D84	4
Eysuvis (US)	Short-term (up to two weeks) treatment of the signs and symptoms of DED	2 weeks	Vehicle	Corneal fluorescein staining score	4
Ikervis (EU)	Treatment of severe keratitis in adult patients with DED, which has not improved despite treatment with tear substitutes	6 months	Vehicle	Corneal fluorescein staining score	2
Hyalein (JP)	Keratoconjunctival epithelial disorder resulting from the following diseases: Intrinsic diseases such as Sjögren's syndrome, Stevens-Johnson syndrome and DED or Extrinsic diseases caused by surgery, drugs, trauma, contact lens wearing, etc	4 weeks	Placebo Artificial tears base	Fluorescein staining score Foreign body sensation score	N/A
Diquas (JP)	Treatment of DED and should be used in patients diagnosed with DED, associated with keratoconjunctival	4 weeks	Sodium hyaluro nate 0.1%	Corneal rose bengal staining score	2

	Indication	Trial duration	Control	Approved Endpoint	Number of pivotal trials
	epithelium disorders that accompany lacrimal fluid abnormality				
Mucosta (JP)	Enhances the production of mucin, a component of tears, to stabilize tear film and thereby improve corneal epithelium damage. It is usually used to treat DED	4 weeks	Sodium hyaluronate 0.1%	Corneal fluorescein staining score Dry Eye Symptoms	2

The comparison further revealed that the trial duration significantly varies, often directly guided by the regulatory requirements of the respective country or the treatment duration required to demonstrate a treatment effect. Looking at the number of trials in which certain endpoints are met, it is rather obvious that there is high variability in trial results and often more than 2 pivotal trials were needed for demonstrating efficacy to the satisfaction of the respective regulators. Even more concerning, signs and symptoms were frequently not met in the same trials requiring additional studies to demonstrate efficacy in both, signs and symptoms, like for Xiidra [70]. Additionally, the demonstration that a certain effect is clinically meaningful seems to be perceived differently in the different regions. Especially the EMA seems to be more critical on this aspect as outlined with the approval of Ikervis and the withdrawal of Restasis and Xiidra in the EU (see section 6).

8.3 Conclusions

In conclusion, the analysis in 3 geographies showed that there is no global medical definition for DED across different regions [22, 23, 24]. This is regarded as one major reason for the heterogenous regulatory requirements worldwide and a key hurdle for harmonization. Especially the different approaches in terms of first-to-treat condition, inflammation versus tear film instability, separate the USA and the EU from Japan [22, 23, 24]. This obstacle is likely the key reason why no harmonized development requirements exist yet. But it also shows that DED is a multifactorial disease which is difficult to adequately characterize [21]. The increasing number of available medical and scientific publications for DED within the last years and the ongoing attempts to find definitions and

discuss different medical and scientific views demonstrates that DED is becoming a focus area in ophthalmic pharmaceutical development. This discussion will certainly be beneficial to overcome current differences and contribute to a common understanding, which is expected to be one important prerequisite to expedite global development approaches to serve patients' needs of a global and growing disease.

Despite the high number of failed clinical trials in DED which did not meet all their prespecified endpoints or could not reproduce findings from earlier development phases, the development of new treatment options seems to be rather exponentially increasing in recent years [78]. Rising public awareness of the disease also large pharmaceutical companies to enter the field of DED drug development. Today these developments focus mainly on the established size of the US DED market, that is still considered the largest market by revenue [9]. So far, no single ongoing development was identified aiming for global DED trials.

As detailed in this thesis, the regulatory requirements for acceptable clinical datasets vary significantly between geographies leading to regional approvals of products which often rejected in other regions, as exemplified for Restasis or Xiidra. One cause is the different perception of the disease being either chronic or relapsing. This results in different expectations for the treatment and especially the duration which ranges from 1 day in the US up to 6 months in the EU [52, 53]. To meet expectation from regulators in both jurisdictions, companies would need to include the EU requirements in parallel into their development plans, meaning either longer or additional studies. This obviously adds additional risk to the US development and substantially increases development costs which is in direct conflict with the interests of the companies. Although new regions like China become more important, it is difficult for companies to prioritize a clearly smaller market like the EU over the US market.

The evaluation of clinical data packages of approved DED drugs also showed that regulatory requirements are not carved in stone. There is room for negotiation with the regulatory authorities e.g., via scientific advice meetings, and a certain level of flexibility to address unmet medical needs. On the one hand, argumentations highlighting e.g., 'clinically meaningful improvement' might also show that regulators are potentially willing to find ways to approve products although all requirements for clinical endpoints might not be

formally met. On the other hand, demonstration that effects are clinically meaningful was shown to be perceived differently in the different regions. Formal regulatory guidelines for developing DED drugs are not yet available in all evaluated geographies.

The current environment is potentially an opportunity for pharmaceutical companies to achieve their goals in specific markets. However, such a situation is not expected to promote harmonization and acceptance in different markets. The example of Xiidra shows that efficacy data was acceptable for the FDA but was not sufficiently convincing to get product approval by the EMA.

Although there is progress in the international DED community, it is not foreseeable that the same standards will be imposed for new DED treatments in the analyzed countries in the near future. Initiatives for discussion between regulatory authorities would need to be required to significantly promote harmonization. The variability of the diagnostic methods and the difficulties of available (bio)markers to reliably indicate disease status or treatment progress is a major obstacle for the scientific progress. The development of new markers and especially their validation of robustness in clinical trials could potentially make the biggest impact on harmonization of accepted endpoints.

With increasing numbers of diagnosed patients and continued interest of the pharmaceutical industry, DED is becoming more and more visible as a serious disease. This surely will be a driving force to bring innovation to the field of DED treatments, force regulators to adjust their expectations and finally provide DED patients with superior therapeutic options to improve their disease condition and subsequently their quality of life.

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Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Schifferstadt,

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Johannes Korward