Special Article

Report of the TFOS/ARVO Symposium on Global Treatments for Dry Eye Disease: An Unmet Need

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ABSTRACT In September 2010, a Symposium in Florence, Italy, was held to address the unmet need for global treatments for dry eye disease (DED). It was sponsored by The Tear Film & Ocular Surface Society (TFOS; www.TearFilm.org) and co-sponsored by the Association for Research in Vision & Ophthalmology (www.arvo.org). The Symposium objectives were two-fold: first, to discuss accepted and emerging clinical endpoints of DED with regulatory experts from around the world; and second, to consider how to improve clinical trials of treatments for DED. The Symposium focused on the personal and collective burden of DED, as well as the developmental and regulatory challenges associated with generating new DED therapeutics. This article provides a synopsis of many of the presentations, discussions and recommendations of this Symposium.

KEY WORDS clinical trials, dry eye disease, drug development, Tear Film & Ocular Surface Society

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I. INTRODUCTION

The Tear Film & Ocular Surface Society (TFOS; www.TearFilm.org) sponsored, and the Association for Research in Vision & Ophthalmology (www.arvo.org) co-sponsored, a Symposium in September 2010 in Florence, Italy, to address the unmet need for global treatments for dry eye disease (**DED**). The Symposium was organized by Dr. David A. Sullivan and attended by 210 people. The moderators, speakers and panelists, who were invited by TFOS to participate, are shown in Table 1. The specific topics to be addressed are listed in Table 2. The overall Symposium objectives were two-fold: first, to discuss accepted and emerging clinical endpoints of DED with regulatory experts from around the world; and second, to consider how to improve clinical trials of treatments for DED. The Symposium focused on the personal and collective burden of DED, as well as the developmental and regulatory challenges associated with generating new DED therapeutics. This article summarizes many of the presentations, discussions, and recommendations of this Symposium.

II. DRY EYE DISEASE: THE PROBLEM

A. The Voice of a Patient

"Welcome to my world," said Katherine Morland Hammitt, the Vice President of Research of the Sjögren's Syndrome Foundation. "At night my dry eye disease causes my eyelids to stick together and interferes with sleep. During the day, my dry eye limits reading, working on the computer, and watching television. And during both night and day my dry eye gives me constant pain, makes driving difficult, and interferes with my career and hobbies."

Ms. Hammitt, who also has Sjögren syndrome, noted: "I can't cry…what makes us more human than that?" Indeed, the most common symptom experienced by Sjögren syndrome patients is dry eye, according to a 2007 survey.[1] Ms. Hammitt continued: "One of my favorite cartoons shows a psychiatrist telling a Sjögren syndrome patient, 'It's not in your head, it's all in your body.' The reason this is so funny, or sad, is that so many of us are labeled hypochondriacs by health professionals, family,

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and friends before we get a diagnosis, and for some, that continues after diagnosis because others don't understand and can't relate to our disease…We desperately need answers, better treatments, and ways to get new treatments to dry eye patients."

B. A Global Perspective

Dry eye disease is one of the leading causes of patient visits to eye care practitioners in the United States. This disease afflicts around 5 million older Americans, predominantly women. Tens of millions more Americans may have a less severe manifestation of the disease.[2-4] Dry eye is also one of the most prevalent eye diseases outside the United States, especially in Asia, where as many as 20-50% of the population of older people in some areas may be affected.[2] Dry eye disease is characterized by a vicious cycle of hyperosmolarity and chronic inflammation, which can lead to increased friction and eventual damage to the ocular surface.[5-7]

Important risk factors for the development of DED, as reviewed by Dr. Debra A. Schaumberg, include older age, female sex, reduced androgen levels, and an imbalance in the dietary intake of omega 3 and omega 6 fatty acids.[2-4,8,9] Additional risk factors for DED in women include exogenous estrogen use (ie, hormone replacement therapy),[10] and in men include benign prostatic hyperplasia (**BPH**), hypertension, BPH medications, and antidepressants.[4,11]

Emphasizing the significant impact of DED on quality of life, Dr. Schaumberg described the impact of moderate-to-severe DED as comparable to that of dialysis-requiring conditions and severe angina.[12,13] She noted that the visual disturbances of dry eye lead to problems with activities such as reading, computer use, cooking, navigating stairs, professional work performance, and night driving.[2,5,14-16] She further emphasized that dry eye has effects beyond vision, and is associated with role limitations, more pain, lower vitality, and poorer general health.[17]

Overall, DED is a very significant public health problem around the world, and there is as yet no safe and effective treatment available globally.

C. Biological Basis and Clinical Relevance of Ocular Surface Signs

"It is not for a lack of trying" that there are so few DED treatments approved on a global or country-by-country basis, explained Dr. Benjamin D. Sullivan. Demonstrating a measurable and clinically significant improvement requires reductions in both a sign and a symptom of disease. However, the common signs of DED, including Schirmer test results, tear film breakup time (**TFBUT**), ocular surface staining (eg, fluorescein, lissamine green, rose bengal) and meibomian gland dysfunction assessment,[18,19] have poor repeatability in DED patients[20,21]and do not correlate with changes in symptoms.[22-26] Moreover, symptoms may not accurately reflect the severity of DED,[25] in part due to the various levels of nerve injury in DED.[5,27-29] Combined, these factors create substantial challenges to the design of effective inclusion criteria and endpoints in dry eye clinical trials.

Because the underlying processes that initiate and/or promote DED (eg, androgen deficiency, shear stress, inflammation, lipid insufficiency, tear film instability and hyperosmolarity) are beyond the scope of traditional tests, there has been no universally accepted gold standard established for DED.[22-24]

Dr. Benjamin Sullivan noted that to properly reflect disease, we need signs that follow the principal axis of variation of the disease process. The use of tear osmolarity and/or other physically insightful outcome measures (eg, dynamic visual stability, interferometry, friction coefficients, MMP-9, etc.) have the potential to qualify as capable indicators of the disease process. Hyperosmolarity, in particular, is a promising endpoint because it has been shown to have a linear relationship to a composite measure of DED severity.[25,26] Hyperosmolarity, in turn, is a core mechanism of DED,[5,22,26] and alleviation of hyperosmolarity has been shown to precede a decrease in symptoms.[30] The hope is that, as we learn more about new markers, they will permit the generation of clinical endpoints that make it possible to finally test and demonstrate the efficacy of a global treatment for DED.

D. Biological Basis and Clinical Relevance of Ocular Surface Symptoms

Dr. Carolyn Begley pointed out that a paradigm shift in thinking has recently taken place with regard to the cause of symptoms in DED. Over 15 years ago the National Eye Institute / Industry Report defined DED as a "disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.[31] The implication was that an inadequate tear film leads to surface damage, which leads to symptoms, which lead to ocular surface irritation. The idea was that cellular damage causes the symptoms.

Current thinking is expressed in the definition presented by the Definition and Classification Subcommittee of the

Table 1. Moderators, speakers and panelists TFOS/ARVO Symposium on Global Treatments for Dry Eye Disease

Moderators
Reza Dana, MD, MPH, MSc, Professor of Ophthalmology, Harvard Medical School; Senior Scientist, Schepens Eye Research Institute; and Director of the Cornea & Refractive Surgery Service, Massachusetts Eye & Ear Infirmary, Boston, MA, USA
Gary N. Foulks, MD, FACS, Professor of Ophthalmology, Director of Corneal/External Disease and Refractive Surgery, and Assistant Dean for Clinical Trials Research, Kentucky Lions Eye Center, University of Louisville, Louisville, KY, USA
Gary D. Novack, PhD, President, PharmaLogic Development, Inc., San Rafael, CA, USA
Speakers
Stuart B. Abelson, President and Chief Executive Officer, Ora, Andover, MA, USA
Stefano Barabino, MD, PhD, Clinica Oculistica, Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa, Italy
Carolyn G. Begley, OD, MS, Professor of Optometry, School of Optometry, Indiana University, Bloomington, IN, USA
Jean-Sébastien Garrigue, PharmD, MBA, Director, Pharmaceutical Research & Development, Novagali Pharma, Evry, France
Per Gjorstrup, MD, PhD, Chief Medical Officer, Resolvyx Pharmaceuticals, Bedford, MA, USA
Katherine M. Hammitt, Vice President of Research, Sjögren's Syndrome Foundation, Bethesda, MD, USA
Masatsugu Nakamura, PhD, General Manager, Ophthalmic Research Group, Research & Development Center, Santen Pharmaceutical Co, Nara, Japan
Yann Quentric, MSc, Director, Business and Clinical Development, Iris Pharma, La Gaude, France
Anne Marie Salapatek, MSc, PhD, Director, Research & Development and Scientific Affairs, Cetero Research, Mississauga, Ontario, Canada
Debra A. Schaumberg, ScD, OD, MPH, Associate Professor of Ophthalmology, Harvard Medical School and Director of Ophthalmic Epidemiology, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA
Benjamin D. Sullivan, PhD, Chief Scientific Officer, TearLab Corporation, San Diego, CA, USA
David A. Sullivan, PhD, President, Tear Film & Ocular Surface Society; Senior Scientist, Schepens Eye Research Institute; and Associate Professor of Ophthalmology, Harvard Medical School, Boston, MA, USA

Table 1. continues on the following column

Table 1. Moderators, speakers and panelists TFOS/ARVO Symposium on Global Treatments for Dry Eye Disease *(continued)*

Panelists
Vincent H. L. Lee, PhD, DSc, Professor and Director, School of Pharmacy, The Chinese University of Hong Kong, Hong Kong, China
Michael A. Lemp, MD, Clinical Professor of Ophthalmology, Georgetown University and George Washington University, Lake Wales, FL, USA
Jane Moseley, MB, MSc, MFPM, Ophthalmologist and Scientific Administrator, Scientific Advice H-HM-SA, Human Medicines Special Areas, Human Medicines Development and Evaluation, European Medicines Agency, London, UK
Clarice Alegre Petramale, MD, Regulatory Expert for Clinical Trials, ANVISA (Agência Nacional de Vigilância Sanitária), Brasilia, Brazil
Tony Whittaker, PhD, Manager, Regulatory Affairs and Quality, Commercial Eyes, Abbotsford, Australia
Kerstin Wickström, PhD, Senior Expert, Läkemedelsverket, Medical Products Agency, Uppsala, Sweden
Michelle Dalton, ELS, a medical writing and editing specialist from Dalton & Associates (Reading, PA), was invited by TFOS to take notes during this Symposium and to summarize the material after the meeting.

International Dry Eye WorkShop Report (2007): DED is "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[5] As noted by Dr. Begley, the core mechanisms of this definition are tear film instability and hyperosmolarity, and the stress they cause to the ocular surface and nerves. Stress, which may lead to the symptoms of ocular discomfort, is now the key concept. In contrast, cellular damage can be a downstream effect.

The stress of tear instability and tear breakup may result in stimulation of corneal nociceptors and visual disturbances.[32-34] In addition, hyperosmolar stress can lead to inflammation, disruption of the corneal neural feedback loop, stimulation of corneal nerves, accumulation of inflammatory mediators in tears, and the symptoms of DED. The threshold for corneal sensation is ~450mOsm/kg, but local levels of tear film osmolarity could rise as high as ~ 800mOsm/kg with tear film breakup in dry eye."[35]

In effect, the stress of tear film instability and hyperosmolarity is one cause of dry eye symptoms. This understanding may help in the selection of clinical endpoints of future clinical trials to evaluate new DED treatments.

Table 2. TFOS / ARVO topics addressed by the speakers and panelists

David A. Sullivan: Introduce the objectives of the Symposium.
Katherine M. Hammitt: Give a patient's perspective of dry eye syndrome and its impact on quality of life; comment on the unmet need for new dry eye therapies.
Debra A. Schaumberg: Review the definition, overall classification, global prevalence, economic burden, quality of life impact, and public health significance of dry eye syndrome; comment on the unmet need for new dry eye treatments.
Benjamin D. Sullivan: Discuss the biological basis and clinical relevance of ocular surface signs in dry eye; indicate, from his perspective, the most important signs to include in clinical trials of dry eye therapies.
Carolyn G. Begley: Discuss the biological basis of ocular surface symptoms in dry eye; indicate, from her perspective, the most important symptoms to include in clinical trials of dry eye therapies.
Per Gjorstrup, Jean-Sébastien Garrigue and Masatsugu Nakamura: Present the scientific, translational and clinical challenges faced by each of their companies in the development of a dry eye treatment; comment on how this developmental process could be improved in the future.
Stuart B. Abelson, Yann Quentric, Anne Marie Salapatek: Describe the clinical trial and regulatory challenges faced by each of their companies in the development of a dry eye treatment; comment on how this developmental process could be improved in the future.
Vincent H. L. Lee, Michael A. Lemp, Jane Moseley, Clarice Alegre Petramale, Tony Whittaker and Kerstin Wickström: Discuss American, Asian, Australian, and European, regulatory processes. The regulatory official from Africa was unable to participate.

III. DRY EYE SYNDROME: THE TREATMENT CHALLENGE

When Dr. Per Gjorstrup first considered developing a DED treatment several years ago, he realized that it would be difficult for many reasons. In designing a clinical study, researchers choose the most likely predictive preclinical models and target cells based on understanding of the clinical pathology of a disease. However, these types of translational paradigms are not yet established for DED, which makes the clinical efficacy of selected candidates somewhat unpredictable. Dr. Gjorstrup noted that "no drug that has been prospectively evaluated in a set of preclinical models has then gone on to achieve label approval for the treatment of DED." Given this background, Dr. Gjorstrup was not surprised that a number of "investors see DED as a money pit, where nothing is predictable and nothing has worked."

"Drug development is all about getting a good clinical trial protocol," Dr. Gjorstrup said. This includes selecting inclusion criteria based on patient disease severity, identifying outcome measures linked to therapeutic goals, and defining optimal assessments of intervention efficacy. Such development is greatly facilitated by learning from earlier studies, but very few DED clinical trials have been published.

The Delphi Panel report recommended that at least one sign and one symptom be present for assignment of a patient to a particular DED severity level.[36] However, it is difficult to quantify common DED signs and symptoms by established scales, because their resolution is not particularly rich. In addition, patients use descriptors interchangeably and do not necessarily describe their symptoms the same as others do, but may well mean the same. This elusiveness of common signs and symptoms makes it a challenge to identify appropriate target groups to include in a clinical trial. Moreover, symptoms may be moderate in a given DED population, but signs can be very mild, even absent. Given the limitations of these common DED signs and symptoms, Dr. Gjorstrup observed, "I am not even sure we fully know who the patients are."

Although DED clinical trials in the U.S. emphasize the need to achieve improvement in both signs and symptoms, Dr. Gjorstrup questioned whether we should expect improvement in signs in all patients irrespective of age, gender and duration of DED. Is prevention of further sign progression acceptable, as it is in many other chronic indications (eg, rheumatoid arthritis, multiple sclerosis)? Are some sign assessments as much for safety as for efficacy? Dr. Gjorstrup noted that to date there are no published longitudinal studies to give guidance on inclusion criteria and outcome variables relative to age, sex, duration of disease, etc. It is also not known whether central corneal staining of 2 in a 40-year-old patient has the same meaning as it does in a 70-year-old patient, or whether there is a prognostic value of this staining measurement at either age.

Dr. Jean-Sebastien Garrigue echoed these comments. He reported the outcomes of a 492-patient pivotal clinical trial on improvement in both DED sign (corneal fluorescein staining) and symptoms (trial conducted by Novagali Pharma, Evry, France). After a 6-month treatment period, only 56% of patients showed improvement in both sign and symptom scores. Paradoxically, 15% of patients showed worsening of symptoms despite improvement in signs, and 18% showed improved symptom scores despite worsening of the sign. (These data were presented at the 2011 ARVO meeting.[37]). The considerable variability of symptoms, the poor correlation between these DED signs and symptoms, as well as the lack of published data about minimal clinically important differences, present a difficult challenge in developing and obtaining approval for a DED treatment. This is especially true when improvement in both DED signs and symptoms is an expected outcome in randomized clinical trials investigating new DED therapies.

To improve drug development for DED treatment, Dr. Gjorstrup recommended that we continue to validate preclinical models, build upon existing clinical experience,

Table 3. Questions proposed by participants before the Symposium for panelists' consideration

1) In your region, is Dry Eye Disease recognized as an area of unmet medical need?
2) Considering the heterogeneous population of dry eye disease, are there specific subpopulations that have a higher unmet need?
3) What are acceptable patient populations and study designs for dry eye studies?
4) What are acceptable patient populations and study designs for pivotal phase 3 clinical trials?
   a) Would you consider the appropriate comparator to evaluate safety and efficacy to be the vehicle?
   b) Would the concomitant use of artificial tears be required?
   c) Would USA-based trials be acceptable for registration?
5) What single objective endpoints would be acceptable as a primary endpoint for registration?
   a) For a single objective endpoint, is a statistically significant difference (in the mean or response rate) from vehicle considered acceptable?
   b) If a response criterion is required, what are acceptable response criteria?
      i) Example: 2 point reduction in corneal staining using the Oxford scale (0-6).
      ii) Example: XX mm change in wetting from baseline for Schirmer's.
6) What single subjective endpoint would be acceptable as a primary endpoint for registration?
7) What are acceptable primary endpoints for dry eye studies?
8) For total fluorescein corneal staining (NEI/Industry Workshop Scale, 0-15 points) what minimum difference vs a placebo control is considered clinically important?
9) When co-primary endpoints are used for registration, are there preferred endpoints?
   a) Objective and Subjective endpoint, Example: Schirmer's staining and OSDI
   b) Two objective endpoints
   c) Two subjective endpoints
10) For co-primary endpoints, is a statistically significant difference (in the mean or response rate) from vehicle acceptable for registration?
11) Would a validated biomarker (eg, levels of MMP9 in the tear fluid) be acceptable as a single primary efficacy endpoint and/or as one part of a co-primary endpoint for registration?
   a) Is there a general requirement for validation of a biomarker?
12) At a public meeting, Dr. Wiley Chambers stated that the FDA would accept tear cytokines and osmolarity as objective endpoints for clinical trials in dry eye drug studies as long a improvement was correlated with a measure of patient symptom improvement. Does this change the landscape for trials and improve prospects for successful drug development in this area?
13) What confounding factors are important to control for in dry eye studies?
14) Since dry eye is a chronic condition with many confounding factors, a crossover design might be a good option so that patients could serve as their own control — thoughts? Have they been used?
15) A fellow-eye study design with only one treated eye could work well if patient compliance could be maintained — thoughts? Have they been used?
16) Would the use of a Controlled Adverse Environment (CAE) chamber/model be acceptable for one pivotal phase 3 clinical trial?
17) What would be an acceptable phase 3 pivotal clinical trial duration for the chronic and/or acute treatment of Dry Eye Disease?
18) In addition to adult populations are there specific pediatric populations that we should target for studies?
19) How many pivotal studies are required for approval?
20) What terms does your country use for:
   a) Request to conduct clinical trials (Investigational New Drug [IND])?
   b) Request for marketing approval (New Drug Application [NDA])?
21) IND process:
   a) What is required for your IND — clinical, non-clinical, Chemistry, Manufacturing, and Controls (CMC)?
   b) Are there clinical studies with lowered regulatory requirements (eg, 28 days or shorter, subtherapeutic doses, etc.).
   c) Is this a notification or approval process?
   d) After submission, what is the typical interval until clinical trials may commence?
   e) What flexibility does the Sponsor have on the clinical development process (eg, combined Phase I/II, skipping Phase 2b, etc.).
   f) Are there any particular issues with respect to non-preserved unit dose products?
22) Regulatory partnership
   a) Are there required or suggested meeting times at various development stages (eg, pre-IND, end of Phase 2, etc.)
   b) What are the requirements for a) shipment of investigational material INTO your country, b) FROM your country, and c) regarding non-local sponsorship of investigational studies (eg, no Phase 1 from non-locals)?
23) Guidances:
   a) Do you, in general, follow ICH?
   b) Are your country-specific guidances for development publically available?
   c) Do you have specific guidances for ophthalmic product development?

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Table 3. Questions proposed by participants before the Symposium for panelists' consideration *(continued from previous page)*

- d) Safety: Do you have any direction on non-clinical safety studies for the number of species, duration of treatment, exaggeration and route (eg, ocular vs systemic) for topical ophthalmic products?
- e) Safety: Do you have any direction on the clinical safety requirements for each stage of development or for marketing approval regarding the number of patients and duration of treatment?
- f) EU only: What is the relationship of your country regulatory agency to the EMEA. What are the requirements regarding submission locally vs EMEA (ie, biologics and gene products to EMEA).

24) Ophthalmology
- a) In what organizational group are ophthalmic products reviewed, and by whom?
- b) Are ophthalmic pharmaceuticals and devices in the same division?
- c) Are there special ophthalmic issues? (eg, paucity of clinical pharmacokinetic data)?

25) Ocular surface disease
- a) Do you have any pharmacological treatments for dry eye approved in your country (eg, cyclosporine, diquafasol, hyaluronic acid) and if so, for what indication?
- b) Are there any public precedents or guidances for efficacy for ocular surface disease?
- c) How can TFOS or Sponsors most optimally provide input to you?

require that pivotal clinical trials be placebo-controlled, and assure that outcome measures be independent of intervention. Dr Garrigue pointed out the need to consider and propose new clinical endpoints to regulatory agencies for DED clinical trials. Such endpoints could be biomarkers or signs and symptoms composite endpoints. He further suggested these recommendations could be discussed with agencies (eg, FDA Study Endpoints and Label Development group) by a working committee of experts and company executives (under the auspices of TFOS).

IV. DRY EYE DISEASE: THE REGULATORY CHALLENGE

The clinical trial and regulatory challenges faced by a Contract Research Organization (**CRO**) in the development of a DED treatment are many. As noted by Yann Quentric, these include identifying a potentially responsive population, formulating an optimal study design, and addressing multiple regulatory issues.

Identification of a potentially responsive population requires the recognition that DED has many causes and that clear inclusion and exclusion criteria are essential. Furthermore, the drug's mechanism of action and specific target must be understood. For a DED study design, identification of the relevant clinical endpoints is critical. However, as Mr. Quentric pointed out, this is difficult, given that the common signs and symptoms do not correlate, and other outcome measures, such as biomarkers, must be considered to monitor efficacy of DED treatment. The study design also requires appropriate methodology (eg, Parallel or cross-over? Vehicle or reference? 3 Arms? Wash out? Run in?), standardization (eg, procedures, questionnaires, exams, investigators, environmental factors, in order to reduce variability), assessment of confounding factors (eg, concomitant treatments, other diseases) and statistical analysis. A particular challenge for DED clinical trials involves addressing the hydration effect of a placebo treatment.

International studies face additional challenges. In Europe, difficulties are posed by the lack of Institutional Review Board harmonization between countries, different languages, country-specific approval delays, need for local representatives for non-European Union sponsors, requirement for an Authorization to Import, and the absence of commercial references and treatments (ie, comparators). "To improve the DED treatment development process in Europe," said Mr. Quentric, "we need to select the right population, control the variability, measure the appropriate endpoints, uniformly interpret these outcome variables, and have a reference product available."

These clinical trial and regulatory concerns faced by a CRO in developing dry eye treatments were echoed by Mr. Stuart B. Abelson and Dr. Anne Marie Salapatek.

V. DRY EYE DISEASE: GLOBAL REGULATORY CONSIDERATIONS FOR THE DEVELOPMENT OF DRY EYE THERAPEUTICS

A substantial portion of the Symposium featured a panel discussion concerning clinical endpoints, patient populations, study design, and general questions about DED clinical trials. Representatives of regulatory agencies from around the world were invited. Participating were three regulators and three consultants/academicians presenting their regional regulatory perspectives (Table 1). Meeting attendees proposed questions before the Symposium, which were then provided to the panelists (Table 3).

The current regulatory status of ocular pharmacological therapies is shown in Table 4. In addition to these topically applied agents, systemic pilocarpine (Salagen®, Eisai, Woodcliff Lake, NJ)[38,39]and cevimeline (Evoxac®, Dai Ichi-Sankyo, Parsippany, NJ)[40] are approved for the treatment of symptoms of dry mouth in patients with Sjögren syndrome. Nonetheless, there are relatively few approvals, consistent with the perspective voiced by Ms. Hammitt that relatively few therapeutics are available for patients. The indication statement and pivotal studies to support these approvals vary greatly as well, ranging from various signs (eg, increased Schirmer wetting[41]) to various

Table 4. Regulatory status of ocular pharmacological treatments for dry eye

Product	Country			
	USA	Canada	Japan	Europe
Cyclosporine	Restasis®	Restasis®		—
Hyaluronic Acid	—	—	Hyalein®	—
Diquafosol	—	—	Diquas®	—
Rebamapide	—	—	Mucosta®	—

This information is as of January 2012.

symptoms (Ocular Surface Disease Index, OSDI[42]). To the knowledge of the panel, there are no publicly available guidances for the approval of a pharmacological treatment for dry eye.

All representatives agreed on the desirability of controlled clinical trials to support the approval of novel therapeutics. Some regional differences reflect the health care systems and charters of the regulatory agencies. Although all agencies subscribe to the International Conference on Harmonisation [sic] (**ICH**, http://www.ich.org/) for preclinical, quality, and clinical guidances, the EMA and the Australian Therapeutic Goods Administration (**TGA**) tend to be particularly rigorous in following these guidances, especially with regard to the total number of patients exposed to new medical entities for safety; ie, ICH E1 requires ~1500 total patients to be exposed to the intended marketed dose or greater, whereas FDA typically requires 500. If the treatment is approved elsewhere, China typically requires 200 patients for its pivotal trials.

Consistent with ICH E5, most countries accept data from countries outside of their own region. That said, there is a requirement that the population in the pivotal trials reflects the population in the region in which approval is requested. This typically means that at least some local studies are required.

With respect to dry eye, the Japanese Pharmaceutical and Medical Safety Bureau of the Ministry of Health, Labour and Welfare (Tokyo, Japan) has approved several treatments for "corneal health," primarily on the basis of signs, whereas the U.S. regulators have publicly stated that both a sign and symptom are required for approval of the indication of "treatment of keratoconjunctivitis sicca." It is not clear whether the precedent of the sole approved therapy in the U.S. in 2002 would be relevant today, given today's greater understanding of the assessment of dry eye.

Regional differences exist with regard to pharmacologic vs lubricant type products. Brazilian authorities consider health products as less restrictive than medicinal products (eye drops are considered health products), and, therefore, only safety data are required for approval. As a result, artificial tears are often registered as health products because efficacy could not be shown to be sufficient to warrant a medicinal label. China does not have as many branded medicinal products as other regions. In the U.S., selected lubricants and demulcents are regulated as monographs, and thus no clinical data are required for marketing of the product.

An important regulatory hurdle regards the number of pivotal studies required. In the U.S., since passage of the Kefauver-Harris amendment in 1962, a minimum of two pivotal trials are required for approval. However, some countries, such as Brazil, require only one pivotal study. Australia is consistent with the U.S. and tends to require at least two pivotal studies. In Europe, one single pivotal trial must demonstrate convincing evidence of efficacy and a compelling statistical outcome. However, considering that DED is an area with a history of failures, two pivotal trials, although not necessarily replicates, are strongly recommended.

With respect to the preclinical safety studies required to conduct first-in-human trials of a new therapeutic agent, the panelists cited ICH guidance (ICH M3 R2), although these are not specific for ophthalmics.

While the regulators and representatives present at the Symposium were, by definition, interested in the availability of novel therapeutic agents for DED, in general, the lack of precedent approvals and guidances precluded meaningful answers to most of the questions in Table 3.

VI. CONCLUSION

DED is a substantial global problem, with relatively few approved and demonstrated effective treatments. There are many reasons for this situation, which is most unfortunate for patients. The understanding of dry eye as a real disease, reflective of the greater understanding of ocular surface disease, is relatively recent.[5] This understanding of the prevalence, incidence and chronicity of disease has established the market potential of DED treatments, which has generated investment in the development of novel therapeutics.[43] Many of these investigational therapeutics are based upon new understanding of the disease processes. The manifold clinical signs and symptoms of dry eye and the therapeutic effect of non-medicated vehicles make even controlled clinical trials challenging.[44] Moreover, the lack of dry eye

guidances from regulatory agencies, and only limited precedents, make the investment of resources in DED therapy development risky and problematic. The continued engagement of regulatory officials with ocular surface disease scientists and developers of novel therapies may produce the solutions and lead to successful treatments for millions of underserved DED patients around the world.

ACKNOWLEDGMENTS

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APPENDIX. DISCLOSURES OF FINANCIAL RELATIONSHIPS OF AUTHORS WITH COMPANIES WITH PRODUCTS OR INTERESTS RELATED TO DRY EYE DISEASE.

Stefano Barabino has been a consultant to Bausch & Lomb and Pfizer.

Carolyn Begley has received financial support from Alcon Research, Johnson & Johnson and Vistakon, and has been a consultant to Santen Pharmaceutical.

Michelle Dalton has no proprietary interest in any company with products or interests related to dry eye disease.

Jean-Sébastien Garrigue is an employee of Novagali Pharma.

Per Gjorstrup is an employee of Resolvyx Pharmaceuticals.

Katherine Hammitt has no proprietary interest in any company with products or interests related to dry eye disease.

Masatsugu Nakamura is an employee of Santen Pharmaceutical.

Gary D. Novack is an employee of PharmaLogic Development, Inc, and has been a consultant to Acucela, Axar, Celtic, Inspire, Lux, Merck, Mimetogen, Parion, Santen, SARCode and Senju.

Yann Quentric is an employee of Iris Pharma.

Debra A. Schaumberg has received financial support from Pfizer, and has a personal financial interest in Mimetogen and TearLab Corporation. She has a patent related to dry eye disease, and has been a consultant to Alcon, Allergan, Bausch & Lomb, Celtic, Eleven Biotherapeutics, Inspire, Mimetogen, Pfizer and SARcode.

Benjamin D. Sullivan is an employee of TearLab Corporation, and has a personal financial interest in Lμbris. He is listed on patents related to dry eye disease that are held by Lμbris, TearLab Corporation and the University of California San Diego.

David A. Sullivan has received financial support Alcon, and has a personal financial interest in Lμbris. He has been a consultant to Lμbris and TearLab Corporation, and is listed on patents related to dry eye disease that are held by the Schepens Eye Research Institute.