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MEETING REPORT

A New Vision for the Eye: Unmet Ocular Drug Delivery Needs

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ABBREVIATIONS

AMD	Age related macular degeneration
BCRP	ATP-binding cassette transporter, sub-family G (WHITE), member 2
CMC	Chemistry, manufacturing and controls
CMV	Cytomegalovirus
CNV	Choroidal neovascularization
DME	Diabetic macular edema
DR	Diabetic retinopathy
GCV	Ganciclovir
IOP	Intraocular pressure
IVT	Intravitreal
MEMS	Micro-electro-mechanical systems
MRP	Multidrug resistance-associated protein transporters
OAnT	Organic anion transporters
OCaT	Organic cation transporters
OCT	Optical coherence tomography
PDGF	Platelet-derived growth factor
Pgp	p-glycoprotein
PLGA	Poly-lactic-co-glycolic acid
RPE	Retinal pigment epithelium
TA	Triamcinolone acetonide suspension
VEGF	Vascular endothelial growth factor

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INTRODUCTION

The workshop was kicked-off with an introductory presentation by Dr. Patrick Hughes (Vice President, Drug Delivery, Allergan, Irvine, CA). Dr. Hughes provided a high level but comprehensive overview of the ophthalmic space from disease, ocular physiology and drug delivery perspective.

Briefly, according to Dr. Hughes, visual impairment and blindness lead to significant loss of productivity that is manifested in billions of dollars spent globally. This is a result of several ocular diseases that are amenable to pharmacologic intervention/prevention such as age related macular degeneration (AMD), glaucoma, diabetic retinopathy (DR), and cataract. However, as the average lifespan increases across the world, especially in developed countries, the prevalence of these diseases affecting the anterior and posterior segment of the eye is expected to grow requiring effective delivery strategies for ocular drugs (1). Systemically administered drugs result in poor ocular uptake and poor efficacy-to-safety ratio and hence, topical eye drops have been used over decades to deliver the drug to the eye. However, Dr, Hughes explained, topical delivery is limited by poor ocular bioavailability and ineffective delivery to the back of the eye for vitreoretinal diseases. Poor ocular bioavailability of the drugs when administered topically is related to their poor precorneal retention and poor permeability in the ocular tissues, especially the cornea (2). This results in increased frequency of administration (rarely less than once daily) and hence, various approaches to increase precorneal retention (to enable greater absorption/bioavailability) and permeability have been evaluated. However, for chronic vitreoretinal diseases traditional methods of delivery have been largely ineffective. Hence, direct injections into the vitreous/periocular space of an instant release or sustained release (lipid based and polymeric depots/implants) dosage form is required depending on the physicochemical properties, dose, duration of action and vitreal half-

life of the molecule (3). A number of these delivery platforms have been leveraged to commercialize small molecule and protein/ antibody drugs and several others are in various stages of clinical development.

Despite advancements in the field, there are significant barriers to ocular drug delivery which range from gaps in understanding of disease etiology, lack of robust PK/PD relationship, physiological barriers to anterior and posterior chamber delivery and design, scaling, &control of drug delivery systems. The following sections will discuss the advancements in each of these areas to establish the current state of ocular drug delivery.

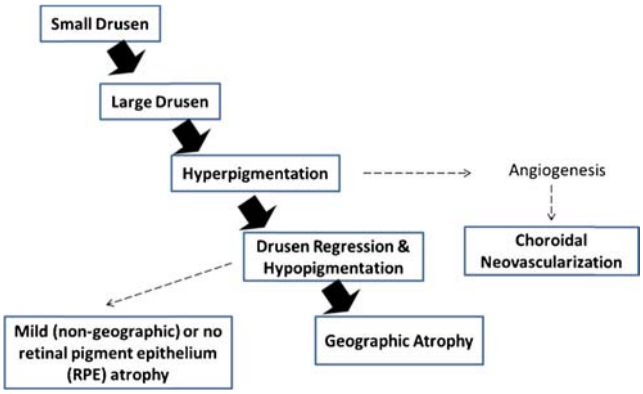

Fig. 1 Evolution of drusen and pathway to geographic atrophy in age-related macular degeneration (AMD).

CLINICAL EXPERIENCE WITH OCULAR DRUGS: UNMET CLINICAL NEEDS

Dr. Karl G. Csaky (Clinical Associate Professor, Department of Ophthalmology, University of Texas – Southwestern) provided an overview of the clinical experience with ocular drugs and identified the unmet clinical needs that would benefit from new molecules and various drug delivery solutions.

Briefly, the structure of the human eye and major diseases which lead to visual loss were discussed by Dr. Csaky including AMD (intermediate drusen, geographic atrophy, choroidal neovascularization (CNV)), diabetic retinopathy (proliferative disease, macular edema) and glaucoma.

Age-Related Macular Degeneration

Dr, Csaky presented that in the United Stated, fifteen million people are currently affected by AMD with two million suffering severe vision loss and the population is expected to double by 2030. Early stage dry AMD is characterized by drusen and hyper- or hypopigmentation of the retinal pigment epithelium (RPE) and advanced AMD can be classified into 2 categories with late stage dry AMD featuring geographic atrophy and neovascular AMD featuring choroidal neovascularization (CNV) (4). The findings from the AREDS, Beaver dam and AREDS II trial on the development of geographic atrophy (Fig. 1) indicated that eyes with drusen and pigmentary alteration developed geographic atrophy, and antioxidant as well as zinc supplementation reduced the risk of advanced AMD and vision loss in high-risk patients. It was also observed that the evolution of atrophy was highly coordinated between eyes. The role of the therapies featuring complement, vitamin A, and ciliary neurotrophic factor (CNTF) were discussed. Various complement pathway inhibitors are in clinical trials for modulating the complement system to treat AMD. They counter multiple genotypic variants of complement pathways, including complement factor H, complement component 2 and 3, and complement factor B and I (4). The visual cycle inhibitors reduce the accumulation of fluorophores such as A2E and lipofuscin in the retinal pigment epithelium (RPE) by interfering with the uptake of retinol into the RPE and subsequent binding to retinol binding protein or conversion to 11-*cis*-retinol (4). Ciliary neurotrophic factor retards the loss of photoreceptor cells during retinal degeneration and is also a member of the IL-6 family of neuropoietic cytokines and hence, affects the survival and differentiation of cells in the nervous system, including retinal cells (5).

The underlying mechanism for neovascular AMD consists of VEGF-mediated angiogenesis and increased vascular permeability. Key clinical data on intravitreal injection of anti-VEGF agents such as ranibizumab (ANCHOR, MARINA, HARBOR, and CATT trials), bevacizumab (CATT trial) or aflibercept (VIEW trial) were reviewed by Dr. Csaky and it was noted that the higher dose did not lead to better anti-VEGF efficacy. The current paradigm (pathophysiology, morphology, hemodynamic properties) for CNV and the diverse morphology (vascular, hypercellular, fibrovascular) of CNV were presented where the OCT (optical coherence tomography) thickness of CNV corresponded to the degree of fibrosis. Visual loss in neovascular AMD could be the result of photoreceptor degeneration, vascular leakage and exudation, or the formation of a neovascular complex. It was highlighted by Dr. Csaky that there is no effective therapy for photoreceptor degeneration. However, anti-VEGF therapy is available to treat leakage and exudation and anti-PDGF therapy (4), designed to weaken the resistance of endothelium to anti-VEGF agents by influencing pericytes, might be suitable for treating the neovascular complex (6,7). Ophtotech's (New York, NY) drug FOVISTA™ (E10030) was presented by Dr. Csaky as an example of anti-PDGF therapy which, when used in combination with ranibizumab, demonstrated superior clinical outcome over ranibizumab alone. The various pathway approaches to neovascular AMD (1) were shared along with the list of drugs that are in clinical development.

Diabetic Retinopathy and Glaucoma

Given the increasing prevalence of diabetes around the globe, the risk of diabetic retinopathy (DR) was discussed by Dr. Csaky. DR could manifest as non-proliferative DR, proliferative DR, or diabetic macular edema (DME). Non-proliferative DR is a chronic condition that occurs over years, typically, with no significant vision loss but can progress into DME or proliferative DR. Proliferative DR, is associated with neovascularization of the retina and high risk of visual loss. DME, on the other hand, occurs in approximately 13% of the DR patients with the risk of developing DME increasing as DR progresses. A treatment regimen and outcomes for ranibizumab (monthly injection) were highlighted by Dr. Csaky where ranibizumab treated subjects demonstrated 3-line gains in vision in almost 40% of patients at 24 months (primary endpoint). Finally, the various mechanistic handles for the control of glaucoma were discussed in Dr. Csaky's presentation. Specifically, agents acting on trabecular meshwork outflow (cholinergic agents, Latrunculins, ROCK inhibitors), agents acting on uveoscleral outflow (prostaglandin analogues, alpha-adrenergic receptor agonists, EP2 agonists, nitric oxide-donating PG F2alpha analogue, and drug eluting punctal plug with latanoprost), and agents acting on inflow (beta-adrenergic receptor blocker, alpha-adrenergic receptor agonists, carbonic anhydrase inhibitors, and siRNA beta-adrenergic receptor antagonist) were highlighted with respect to both currently available treatments and drugs under investigation (4). IOP-lowering drugs, belonging to above mechanisms, that have either been commercialized or that are in in clinical development were briefly reviewed.

Summary and Unmet Medical Needs

In summary, it was emphasized by Dr. Csaky that the largest unmet medical need is in dry AMD. Though therapies exist for neovascular AMD and diabetic retinopathy, they are limited by the need for repeat intravitreal injections and hence, increasing the half-life of drugs administered intravitreally to reduce the frequency of administration will be required. Effective therapies are available for glaucoma administered as topical eye drops but compliance is a potential issue. It was concluded in the discussion that there is a strong need for ocular drug delivery approaches and devices to improve overall therapeutic outcomes and increased patient adherence.

SUSATINED DELIVERY TO THE FRONT OF THE EYE

Dr. Sachin Mittal (Senior Principal Scientist, Formulation Sciences, Merck & Co, Kenilworth, NJ) reviewed various formulation delivery approaches to sustain topical delivery in the eye. The presentation covered key drivers for sustained topical delivery, barriers to topical delivery, and various technology and dosage forms that enable sustained topical delivery to the front of the eye. Briefly, Dr. Mittal explained, the estimated number of visually impaired population in the word is approximately 285 million of which 39 million are blind (8). A majority of the visually impaired and blind population is over >50 year. Further, glaucoma is responsible for only 2% of the visually impaired individuals, but it accounts for 8% of the blind, second only to cataract. Hence, delivery to the front of the eye that also considers the requirements for ageing patients forms a critical component of the treatment/control regimen. However, frequency of administration for topically administered drugs goes up from once a day, as seen with Azalides, to as much as once every 2–4 h as for fluoroquinolones and aminoglycosides, which could be a significant barrier to compliance and therapeutic outcomes (9). The delivery to the front of the eye is challenging due to several barriers to delivery which include lacrimal drainage, short retention on surface, and limited absorption that is influenced by molecular radius and molecule partition coefficient (2,10), as pointed out by Dr. Mittal. Thus, by choosing a mucoadhesive or viscous vehicle or carrier to reduce precorneal drug elimination, one can explore the opportunity to increase retention and enable greater absorption and sustained therapeutic levels (2). Several approaches that enable that shift towards reduced dosing frequency, given an ageing patient population and adherence considerations, were discussed by Dr. Mittal. These approaches are highlighted in Fig. 2 and would aim to: 1) Deliver the active ingredient to the right place at the right time, 2) Improve the ratio of local activity *versus* systemic effects, 3) Reduce the number of installations preferably to once-daily for topical formulations, 4) Be easy to self-administer, 5) Not induce a foreign-body sensation, long-lasting blurring or interference with vision, 6) Not rely on novel and unevaluated ingredients like new chemical entities or difficult to source excipients (unless this is a key element) and preferably excipients should have a drug master file and history of safe use in humans, and 7) Be sterilizable at industrial scale by an established process.

Each approach, along with its basic principle, key components, processing considerations, and resultant bioperformance, was discussed by Dr. Mittal with appropriate examples of products or development candidates. The role of polymers (e.g., hydroxyethyl cellulose, carbopols, gellan gum, xanthum gum) and drug carrier (e.g., poly(styrene-divinyl benzene) sulfonic acid beads also referred to as amberlite™) systems in each of the exemplified products (e.g., Cosopt®, Trusopt®, Betoptic-S®, Azasite®, Timoptic XE®, Zioptan®, Ocusert®, Restasis®, and Cyclokat) was discussed and can be derived in a tabulated format from published literature (2,11). The mechanism of drug release from Betorptic-S suspension is illustrated in Fig. 3.

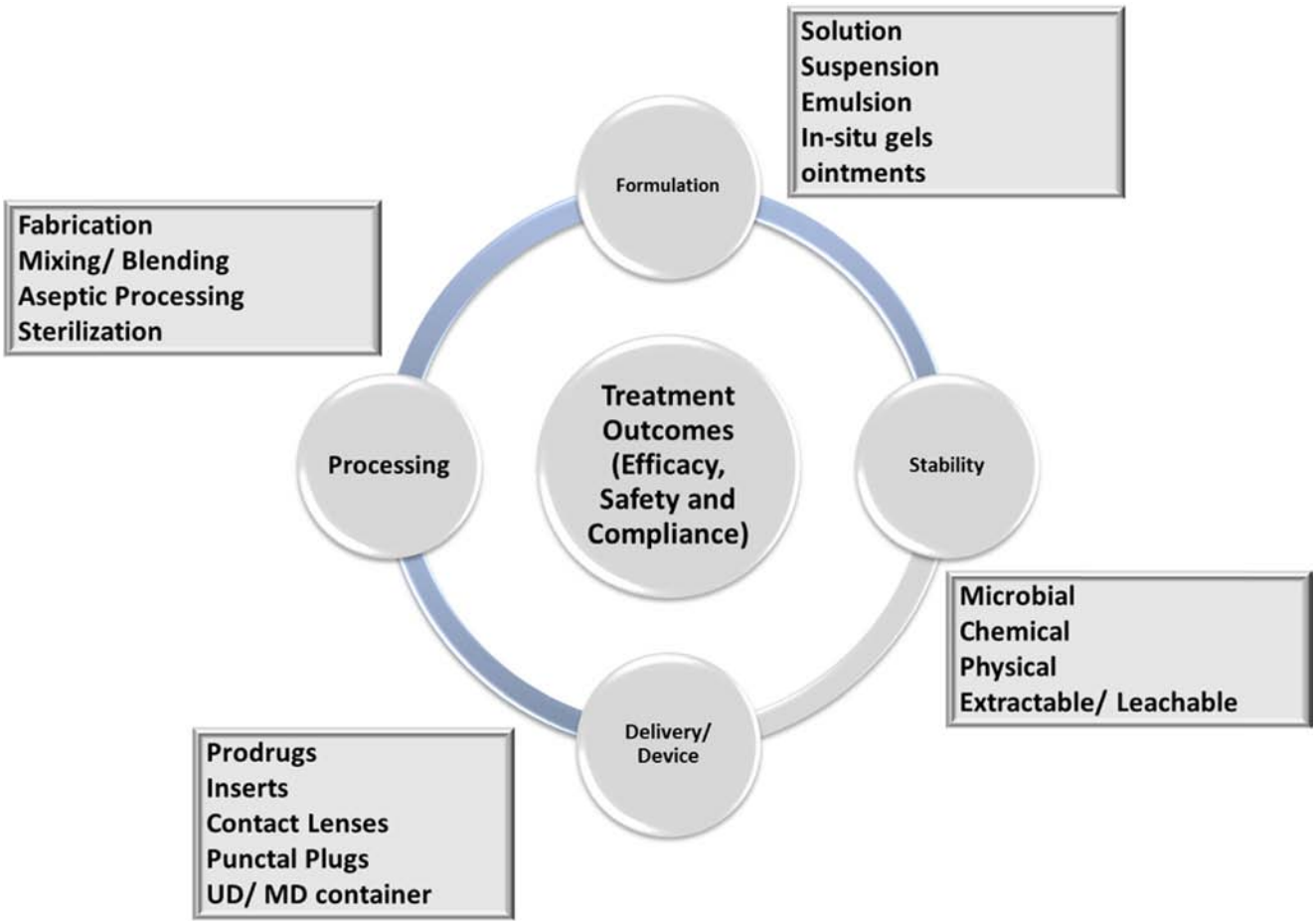

Fig. 2 Translation of target product profile into product attributes.

Dr. Mittal's presentation also provided general guidance for the selection of formulation/drug delivery strategy (Fig. 4) based on duration of action, dose/potency, cost of goods & manufacturing complexity, local tolerability & visual obstruction, and regulatory & market precedence. The quality control and performance evaluation of sustained release formulations is a critical component of the development plan and requires development of *in-vitro* performance/release assays that are predictive of the failure modes and real time performance. Further, the control of polymeric excipients in terms of their critical attributes (molecular weight, inherent viscosity, polydispersity) was also emphasized.

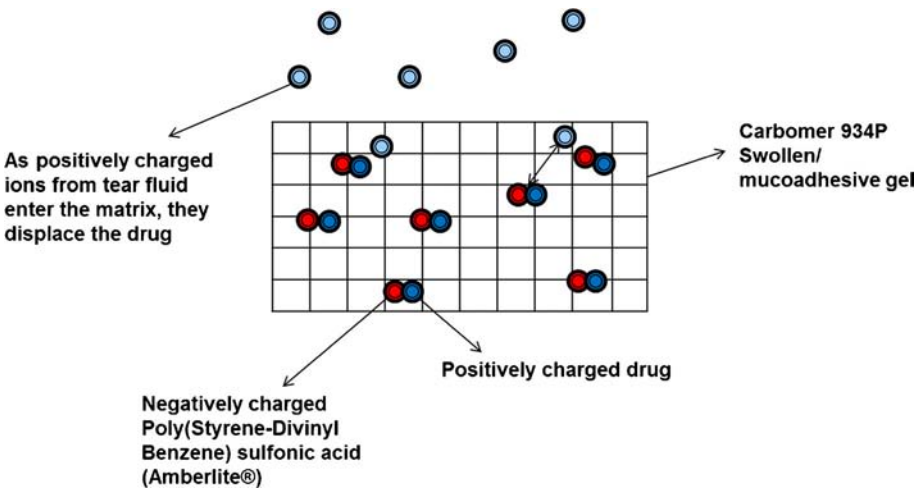

Fig. 3 Schematic of drug release mechanism from Betoptic-S™ suspension to exemplify role of polymers and drug carriers in sustained topical delivery. The factors influencing drug release/ bioavailability include particle size, polydispersity, pH, zeta potential and viscosity of the gel matrix.

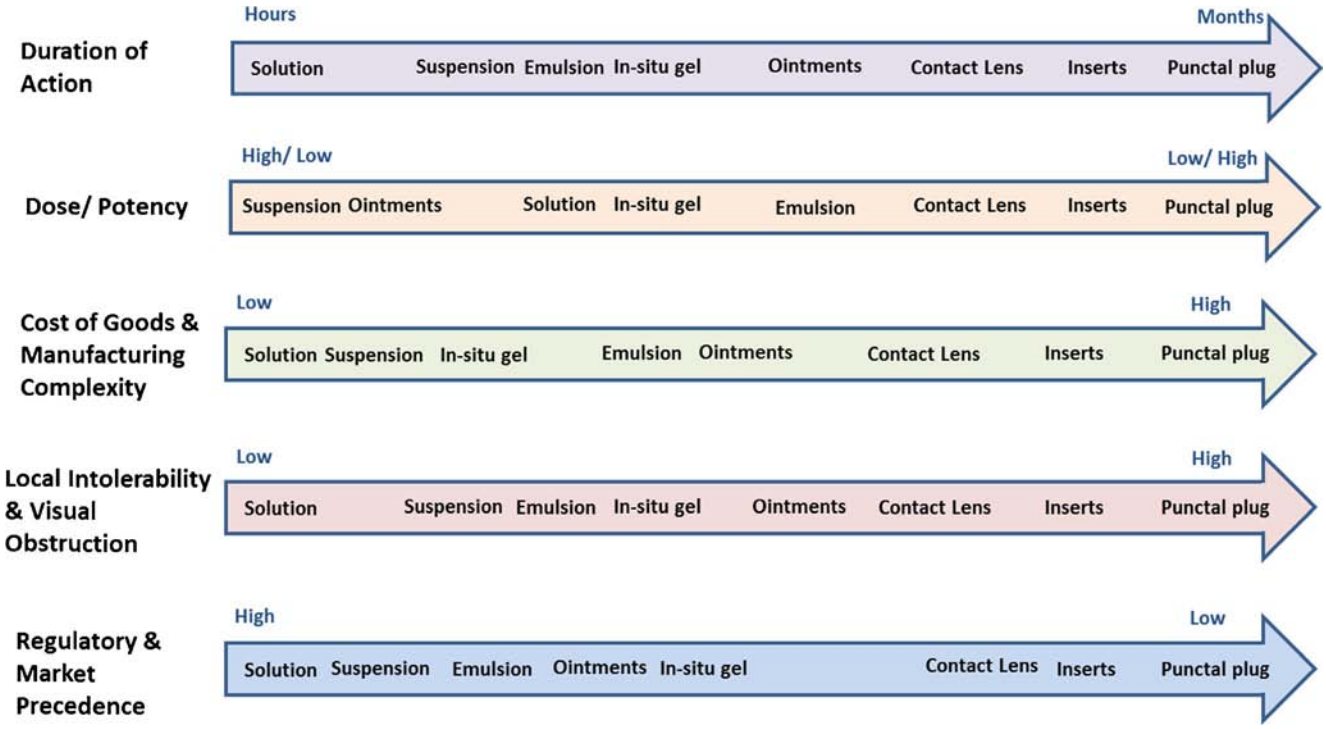

Fig. 4 Multifactorial technology selection criteria and recommendation.

It was concluded by Dr. Mittal that sustained delivery to the front of the eye is challenging due to short precorneal residence time, but several dosage forms (solutions, suspensions, emulsions, *in-situ* gels, and ointments) offer promising opportunities for sustained delivery over a few hours to a day. Despite advances, sustained delivery to the front of the eye for several days or longer is not considered feasible with current options, and finally some of the novel systems such as contact lens and punctal plug offer promise for the future to extend delivery up to a few weeks/months.

SUSTAINED DELIVERY TO THE BACK OF THE EYE

Sustained Delivery to the Back of the Eye- Refillable Devices

The following is a synopsis of the presentation by Alan Weiner (DrugDel Consulting, LLC) on sustained delivery to the back of the eye-refillable devices. Dr. Weiner first pointed out that the design of the delivery system for back of the eye diseases should primarily be influenced by the medical condition being treated and hence major factors influencing device design include patient needs, and clinical and health care provider expectations. However in addition, the cost of treatment those 3rd party payers are willing to pay and challenges in manufacturing and regulatory expectations drive the design of the delivery system. The compliance and acceptability by patient is dependent upon a variety of factors such as extent of vision loss, complexity and invasive nature of the dosing, and the degree of efficacy and safety risk with the treatment. The duration of treatment achievable by the device further drives the acceptability of the treatment based upon the above factors. For example, a patient with a greater degree of vision loss may be willing to accept a more invasive surgical procedure for a device that provides a 6 month to 1 year delivery duration if the safety and efficacy profile is significantly better. Thus design of the device and/or delivery system will have to take all of the above factors into consideration for achieving the target product profile.

A recent approach for drug delivery to the back of the eye is refillable non-eroding reservoir based devices that constantly infuse or inject drug to the target area of the eye with an implanted cannula, as presented by Dr. Weiner. This approach allows finely controlled and tunable delivery rate, and long term delivery with potential for alternative pulsatile delivery profiles with less invasive mode following initial implantation. This is not a totally novel approach as refillable implantable pumps have been used for many years for insulin delivery in diabetics and the hardware and software to achieve this are well known. However before the discussion on refillable reservoir type devices, different types of delivery systems employed in this area were reviewed by Dr. Weiner.

Depot injections utilizing suspensions, gels and liposomes can achieve days up to few weeks release duration while erodible or non-erodible implants and reservoir systems are needed for months to multiple year duration. All anatomical areas of

the eye have been explored and investigated as administration sites with varying degree of success (12). Various routes of administration such as topical, intravitreal/intravitreous (IVT), subtenon, subconjunctival, suprachoroidal and subretinal may offer different advantages such as ease of administration for topical dosing but face the challenges of pharmacokinetic limitations such as rapid clearance. A variety of drug delivery systems such as punctual plugs, polymeric inserts and intralens systems have been designed and investigated due to ease of topical administration. However due to very small amount of drug reaching target tissues, limited duration of release, and corneal sensitivity to foreign objects very few systems have progressed to Phase 3 such as contact lens containing Ketotifen by Vistakon (Jacksonville, FL) and Eyegate's (Waltham, MA) iontophoretic delivery system. There are several iontophoretic technologies in preclinical and clinical stages of investigation and have demonstrated higher sustained drug levels but of short duration compared to passive drug delivery and lacked convincing delivery to posterior of the eye (13). However, none of the iontophoretic systems has achieved regulatory approval so far. Several drug-polymer matrix systems have been studied as implants by subconjunctival route for back of the eye delivery in preclinical and clinical studies and have been only moderately successful as only a small fraction of released drug reaches choroid and retina while majority is released into the systemic circulation (12,13).

The most fruitful area of research and development has been erodible and non-erodible implants administrated directly into the vitreous or implanted such that drug release occurs directly into the vitreous, according to Dr. Weiner. This mode of dosing ensures direct drug delivery to target tissues, choroid and retina, with lower systemic exposure. However due to the invasive nature of the dosing and risk for infection, inflammation, and inability to easily retrieve the delivery system, there is a need for a long acting system that is smaller in size and composed of materials that are biocompatible with ocular tissue and environment. The release duration by direct IVT route will be influenced by the extent of clearance by the anterior route and diffusion across back of the eye that is influenced primarily by molecular weight, partition and diffusion coefficient of the drug and to a lesser extent by vascular clearance (14). Example of a commercial erodible PLGA matrix based IVT system includes Ozurdex by Allergan and several are in different clinical studies. These systems use PLGA as a release controlling polymer which can undergo bulk erosion, and to some extent, release kinetics is modulated by the geometry of the implant (surface area/volume ratio). The non-erodible multi-year delivery systems such as Iluvein (Psivida/Alimera) are reservoir type devices with non-biodegradable polymer as release controlling membrane. If one compares the physical size and design of Vitrasert, Retisert and Iluvein, which are all reservoir type devices, focus has been on reducing the size, increasing the release duration and transitioning from surgical to injectable devices, as emphasized by Dr. Weiner. Due to the advances in material science and nanotechnology, devices with nanochannels and nanoporous materials are being investigated as drug delivery systems to modulate release properties. Despite the success of the IVT devices, the smaller size limits the dose of the drug that can be delivered and consequently, these systems are limited to potent drugs with daily doses of 1 μg/day to achieve 6 month delivery duration with a device that can be injected with a rather large 21 gauge needle.

The limitation of dose for IVT devices has led scientist to explore other routes of administration such as subtenon, intracapsular or suprachoroidal that allows a larger device to be implanted or a rather large volume delivery, Dr. Weiner further explained. An alternative solution to this challenge would be refillable non-eroding reservoir based devices that constantly infuse or inject drug to the target area of the eye with an implanted cannula. The reservoirs allow finely controlled and tunable delivery rate, long term delivery with potential for alternative pulsatile delivery profiles with less invasive mode following initial implantation. The key considerations for ocular refillable device would be location for the reservoir, port location, pumping mechanism, size and fill capacity optimization, fluid hydrodynamics and addressing contamination concerns. Drug potency, aqueous solubility and delivery duration will influence the fluid pumping rate for achieving desired dose in small volumes. The device chamber (static *versus* dynamic) needs to allow for volume changes, and the presence of separate injection and refill ports can be engineered to overcome fluid flow challenges due to changing fluid pressure and volume of the chamber. Several designs have been explored with either passive flow or active pumping mechanism designed with micro-electro-mechanical systems (MEMS). These pumps and reservoir have a cannula that is inserted in the pars plana area for unobstructed delivery of the drug. Two leading systems, Forsight Vision and Replenish, are currently under clinical investigation.

In summary, Dr. Weiner presented that safe and effective drug delivery systems based upon erodible and non-erodible matrix and reservoir systems have been successfully developed and commercialized. The preferred route of administration is intravitreal and small potent molecules such as steroids are delivered for durations up to multiple years. Reservoir systems, specifically the refillable with pumping mechanism, offer the opportunity of finer release control, reliability and ability to deliver macromolecules in aqueous solutions. However, the unique challenges in design need to be addressed for successful commercialization.

New Advances in Drug Delivery to the Back of the Eye

This is a summary of a presentation by Dr Henry F. Edelhauser (Professor, Emory Eye Center, Emory University) on his recent

work in collaboration with Samir Patel and Mark Prausnitz (Emory University and Clearside Biomedical). The research was funded by Alcon and Clearside Biomedical. All possible routes of ocular administration (intravitreal, subconjunctival, subtenon, suprachoroidal and topical) have been studied for retinal diseases (15), as discussed by Dr. Edelhauser. IVT administration of drugs has been the preferred route of dosing due to the direct access to the diseased tissues, retina and choroid. However time dependent images of drug particle distribution in the vitreous in enucleated eye following IVT dosing with triamcinolone acetonide suspension (TA) show slow spread and lack of uniform drug distribution in viscous vitreous. Liquefied and/or non-uniform vitreous exhibiting syneresis in an ageing patient may further impact the distribution of drug in vitreous upon IVT dosing. Additional concerns include, the invasive nature of IVT dosing and limited volume that can be injected, and as a result, alternatives such as transscleral drug delivery have been investigated for back of the eye diseases.

Human sclera is a fibrous avascular connective tissue with minimal thickness (0.1–0.25 mm) at limbus, and then sclera's thickness increases as one maps sclera towards the optic nerve (16), as reviewed by Dr. Edelhauser. Due to its large total surface area (16–17 cm^2), sclera can serve as a large site for drug administration and it is relatively easily accessible. The underlying tissues (sclera, choroid, bruch's membrane and RPS) are considered to be minor diffusional barriers while the rich conjunctival/episcleral and choroidal blood flow and bulk fluid flow may be major dynamic barriers to transscleral drug delivery. Dr. Edelhauser presented that *in vitro* scleral permeability studies have shown that scleral permeability is inversely proportional to log of molecular weight and relatively independent of partition coefficient suggesting a pore pathway for transscleral diffusion (17). These results are consistent with the characteristics of sclera as a connective tissue rather than a homogenous lipophilic membrane. Also, the transport rate of liposomal doxorubicin compared to true solution and nanoparticles showed that liposomal drug having 10-fold lower transport rate indicating size dependent permeability. *In vitro* human transscleral permeability of custom made Oregon Green labeled TA showed rapid and linear penetration of the dye into and across sclera after subtenon injection (18). Fluorophotometry of the eye in live rabbits allowed real-time imaging of kinetics of oregon green dye uptake across sclera into various tissues of the eye after subtenon injection. The concentration of the dye as a function of distance from the detector and as a function of time showed increasing levels in the retina and choroid with lower levels mid-vitreous and higher levels in the cornea. This distribution became more diffuse and spread out in mid-vitreous post-euthanasia after subtenon injection suggesting that lack of blood flow alters the ocular drug distribution and the important role of episcleral blood flow in transscleral drug delivery.

According to Dr. Edelhauser, microneedles have been considered as a less invasive approach for transscleral drug delivery compared to IVT particularly if the needle gauge can be larger and of limited needle length to prevent breaching of choroid. The hollow microneedles (33G) of shorter length (750 μm) have been designed to deliver larger volume of viscous solutions, suspensions and gels into the sclera and deposit the drug in the suprachoroidal space without breaching choroid and retina to enter vitreous. The microneedles can deliver suspension with particles sized at 20 nm, 500 nm and 1 μm into the suprachoroidal space as evidenced by fluorescence imaging of the enucleated eye post-injection. However, the particles spread in the suprachoroidal space laterally around the globe rather than penetrating deeper into the vitreous across choroid and retina. Real time video imaging of black indian ink delivered by microneedles demonstrated similarly initial deposition in the suprachoroidal region followed by slow penetration into choroid. The question is, do the particles remain in the suprachoroidal space and for how long to provide an effective depot since larger particles shouldn't penetrate across choroid. Using fluorescently labeled particles and flourophotometry, 10 μm particles appeared to be concentrated in region adjacent to choroid/retina for a long duration of 31–35 days with none in vitreous or front of the eye. Similar results were observed with particles of different sizes however there seems to be no simple correlation between fluorescence intensity and particle size. Whole rabbit eye imaging showed particles of 500 nm and 10 μm at the injection site, and suprachoriodal space for 4 weeks and 2 months respectively. These studies provided the proof of concept in preclinical models of particulate delivery and depot formation with microneedle's injection through sclera, as pointed out by Dr. Edelhauser. The preclinical studies in rabbit with suprachoroidal (Triesence) and IVT TA (4 mg in 100 μl) injections showed significantly higher exposure to choroid and sclera and very low exposure to front of eye tissues with suprachoroidal injection compared to IVT. This is potentially a significant clinical benefit as this mode retains drug at the site of inflammation and away from anterior of the eye where side effects of IOP and cataract may occur with TA. In a pig inflammation model, the inflammation dose response cure for suprachoriodal dosing was similar to IVT dosing but with 10-fold lower dose and earlier onset. Dr. Edelhauser mentioned that Clearside Biomedical is currently evaluating the microinjection device as a non-surgical option for drug delivery in clinic. Open label safety of suprachoroidal bevacizumab by mirconeedle transscleral injection has been completed with similar tolerability to IVT dose. In summary, Dr. Edelhauser demonstrated that microneedles can deliver a variety of drug delivery materials into the suprachoroidal space and target the chorioretinal space more effectively than IVT and sustained delivery can potentially be achieved due to depot formation. The clinical efficacy of such a delivery system, however, has

not been demonstrated, and superiority of pharmacokinetic exposure of chorioretinal area and effective drug delivery needs to be fully assessed.

CASE STUDIES OF OCULAR DRUG DELIVERY SYSTEMS

Vitrasert: First Non-Biodegradable Sustained Release Device for the Eye

Dr. Paul Ashton (President and Chief Executive Officer, pSidiva) shared the experience of developing first sustained release implant, Vitrasert, as an example to illustrate how drug delivery played a transformational role by filling in a therapy gap. According to Dr. Ashton, Cytomegalovirus (CMV) retinitis is an inflammation of the retina of the eye that could lead to blindness and affects predominantly people with severely compromised immune system. In 1990s, ganciclovir (GCV) was available as an effective treatment for CMV but required to be used at high doses which could cause life-threatening neutropenia (19). Localized intravitreal injection of GCV would work but frequent injection (weekly or every 2 weeks) was required (20). Vitrasert was designed to resolve the issue by borrowing existing technology to make a sustained release device which could be implanted in the eye by following a standard surgical procedure (https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/67/vitrasert-implant.).

Dr. Ashton further explained that the implant consisted of an impermeable layer, a drug core and a permeable layer and GCV was released at a constant low rate for 169 days. In the first clinical trial that included CMV patients who were no longer tolerant of systemic therapy, all 13 eyes resolved CMV and 9 eyes showed stable or improved visual acuity while side effects included retinal detachment and vitreous hemorrhage. Vitrasert was approved by FDA in 1996 and by EU in 1997. As a non-biodegradable ocular device, it was later followed by Retisert for uveitis in 2005 and Illuvein for DME in 2012 (http://www.psivida.com/products-retisert.html and http://www.psivida.com/products-iluvien.html.).

Tethadur Technology: Bridging the Gap Between Biologic Evolution and Therapy

Tethadur technology has recently been developed by pSidiva, as discussed by Dr. Ashton. It is a drug delivery platform that is designed to fill in current therapy as well as patent gap for biologics by utilizing material science. It is based on porous silicon which has honeycomb structure with tunable properties. Proteins easily "stick" to the material and the nanostructured pores ensure sufficient surface area for protein loading and can be tailored over a wide range (2.5 to 40 nm pore size) to accommodate proteins of various size. Surface chemistry can also be modified for loading proteins with different properties. Once loaded into the porous particles, proteins can be stabilized with minimum aggregation by structural confinement and released in a sustained and controlled manner. A Thethadur-based formulation would be a pre-loaded syringe. After adding water to the lyophilized protein or peptide, the drug solution can be drawn into the syringe to form a Tethadur based suspension and dosed 8 min later.

The utility of Tethadur technology in sustained delivery of biologics was demonstrated by Dr. Ashton with two antibody drugs: Avastin and Herceptin. Both antibodies were shown to be continuously released in a nearly linear fashion for 70 days with low burst and 90–100% completion. The release rate could be adjusted by varying pore size. Protein stability post formulation processing was confirmed with SEC-HPLC. To further control protein release rate, a secondary coating of the particles with a polymer solution could be adopted, as shown with proteins including insulin, myoglobin and Lucentis by Dr. Ashton.

ForSight VISION4 Device, Biodegradable Implants and Depot Formulations

Dr. Thierry Nivaggioli (Director, Drug Delivery, Genentech) highlighted a refillable port delivery system (ForSight VISION4 device) for long lasting ocular delivery of ranibizumab (trade name Lucentis). He also discussed the use of a hot melt extrusion process for making protein delivering biodegradable solid implants, and reviewed the efforts on delivering a protein drug using a PLGA-based *in situ* gelling depot system for ocular applications.

OCULAR DRUG DISPOSITION

Dr. Arto Urtti (Professor and Director, Center for Drug Research, University of Helsinki, Finland) spoke on the mechanistic intricacies of ocular drug disposition. Dr. Urtti opened his talk by pointing out that there are several membrane barriers and physiological phenomena that significantly impact the absorption, distribution and clearance of drug molecules when administered into the eye. Collectively, these membrane barriers are classified as 'static barriers' while the physiological phenomena like aqueous humor production and outflow, blinking and nasolacrimal drainage, blood flow and systemic uptake, etc. are classified as 'dynamic barriers' and Dr. Urtti provided a detailed overview of each of these two classes of barriers. He pointed out the need to incorporate all aspects of *in silico* (computational), *in vitro* and *in vivo* studies to further the understanding of the mechanisms of drug disposition and the need for identifying the correct model (*in silico*, *in vitro* or animal) for human scalability. Dr. Urtti then highlighted the different ways of administering a drug into the eye, namely

topical, intravitreal, periocular and even, systemic, where it can distribute from the circulating bloodstream into the eye. For topical ocular delivery, the key aspects that affect the ocular bioavailability of the molecule were discussed. This bioavailability is dependent not only on the properties of the molecule but also on the physiology of the eye. Most importantly, for topical products, it is the corneal permeability that is the key determinant in its performance. This corneal permeability is not always a simple passive transcellular diffusion but may have significant paracellular transport as well as carrier-mediated efflux or influx and similar physicochemical and physiological considerations should be taken for intravitreal delivery. According to Dr. Urtti, vitreal clearance or half-life is a critical indicator of the success of an intravitreally delivered molecule, either a small or a large molecule. Dr. Urtti reviewed the effect of retinal efflux transporters such as Pgp, BCRP, MRP, OAnT, OCaT, etc. in influencing the vitreo-retinal disposition of small molecules (21). He touched briefly on periocular transport where both the understanding and current technology for delivering drugs through this route is far less in comparison to topical or intravitreal. Dr. Urtti concluded his talk by mentioning a few key points about systemic drug delivery with the intent of distribution into the back of the eye. In this aspect, the retina plays a key role. Therefore, the chemical attributes of the molecule, transporters in the retinal pigment epithelium (RPE), passive permeability, blood flow in the retina, etc. all come into play in determining its ultimate success to demonstrate efficacy and safety with an appropriate delivery system.

REGULATORY CONSIDERATIONS

The final speaker for the workshop was Dr. Lewis Gryziewicz (Senior Director, Global Regulatory Affairs, Allergan) who highlighted an array of regulatory aspects that are necessary to consider for the approval of an ocular drug product. With the growing trend of several ocular therapeutics intended for the back of the eye, he rightly pointed out that many of them are sustained drug release platforms and, hence, involve some type of device in the product. These should therefore be classified as 'combination products'. Dr. Gryziewicz discussed a few examples of combination products including pre-filled syringes with an applicator, refillable devices in the eye. He also extensively elaborated on the role of the Office of the Combination Products within the FDA. Dr. Gryziewicz focused on FDA's definition of a combination product, its rules and guidance with respect to manufacturing of the products. Most importantly, his regulatory opinion was "drugs are regulated as drugs, devices as devices". In other words, prior to combining a drug with a device, FDA expects manufacturers to apply the appropriate GMP requirements to each "constituent part". After combining a drug with a device, both regulations apply, but manufacturers may use one set of regulations or the other as appropriate to their operation. Dr. Gryziewicz specifically focused on the intricate details and specific sub-rules of following these GMP guidelines that are central to regulating both the drug and the device and further talked about the critical issue of design control and explained the domain of its applicability (Fig. 5).

FDA's draft guidance on post-approval modifications to a combination product (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336230.pdf) was reviewed which can be critical for the eventual transition into the next generation version of the product.. European Union's draft guidance of combination products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003689.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf) was also

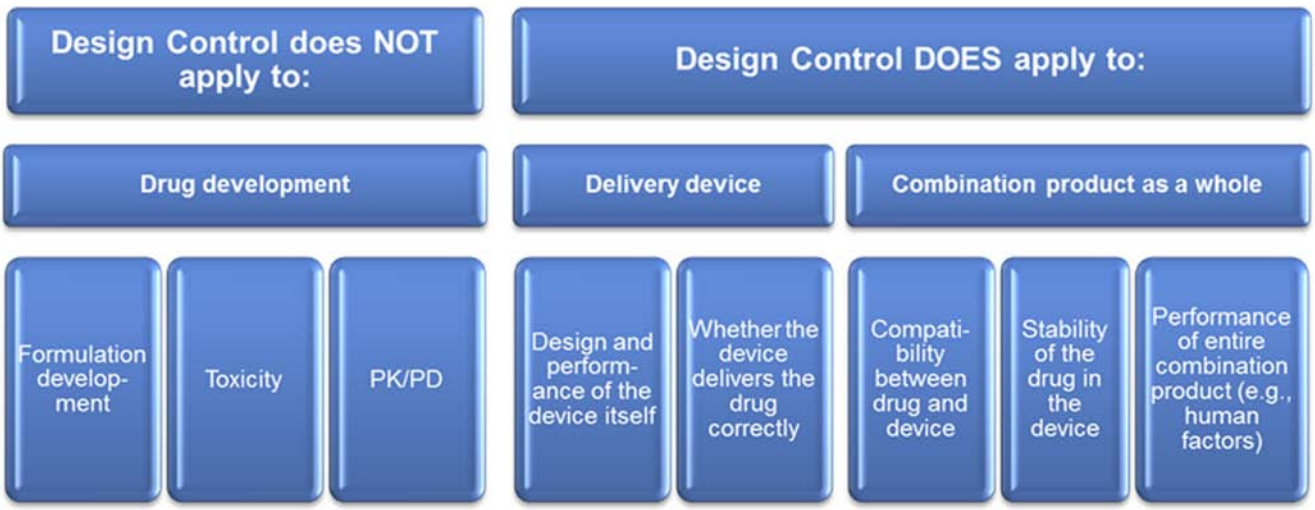

Fig. 5 Graphical representation on FDA's position on the applicability of design Controls.

explained, especially regarding its similarities and difference with that of the FDA. Finally, Dr. Gryziewicz concluded his talk on the specific FDA guidance on pens, jets and related injectors, as these devices have become critical to the success of a modern drug-device combination product for delivering ocular therapeutics.

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