

# Preface

Age-related macular degeneration and macular edema are major vision-threatening disorders of the back of the eye. The first therapeutic agents for treating these diseases, Macugen<sup>TM</sup> (Pfizer, a nucleic acid-based drug), Lucentis<sup>TM</sup> (Genentech; a protein drug), and Ozurdex<sup>TM</sup> (Allergan; a small molecule drug in a biodegradable, injectable implant) were approved by the US FDA in 2004, 2006, and 2009, respectively. Lucentis is already a billion-dollar product. With the success of Lucentis, there is an escalated activity for drug development for the back of the eye. Also, as evident earlier, a variety of therapeutic agents including nucleic acids, protein drugs, and small molecules are making inroads into the emerging back of the eye drug product market. Further, some unique delivery systems including surgically placed and injectable non-degradable implants have pioneered zero-order release of small molecule drugs for treating back of the eye diseases. Vitrasert<sup>TM</sup> and Retisert<sup>TM</sup>, surgically placed intravitreal implants, were approved in 1996 and 2005, respectively, for treating cytomegalovirus retinitis and chronic non-infectious uveitis. Iluvien<sup>TM</sup>, an injectable, third-generation non-degradable implant for the eye, is in late stage clinical trials for treating diabetic macular edema. In addition, cell encapsulating implants for long-term delivery of growth factors are undergoing late-phase clinical trials for treating age-related macular degeneration. It is anticipated that drug development for the back of the eye will take a center stage in ophthalmic drug product development during the next decade. Currently available textbooks do not address drug delivery and product development challenges and the selection of delivery systems for various classes of therapeutic agents in a systematic manner. To cater to this unmet need, we undertook the task of preparing a comprehensive textbook in the area of drug product development for the back of the eye, authored by ocular drug delivery experts, representing academic, clinical, and industrial organizations.

After discovering a drug molecule with therapeutic activity in the back of the eye tissues, a drug delivery scientist is presented with a multitude of options for routes of drug delivery and choice of delivery system. Chapter 1 presents a rational approach for selecting routes of administration and delivery systems for the back of the eye. Routine ocular pharmacokinetic studies are not yet viable in humans for the purpose of back of the eye drug product development, necessitating the use of

preclinical models for such studies. Since eye tissue sampling cannot be performed continuously, several animals are sacrificed for a single pharmacokinetic study. Microdialysis of ocular fluids and fluorophotometry, two alternatives that provide full pharmacokinetic profile with limited number of animals, are presented in Chapters 2 and 3, respectively.

Chapters 4–8 discuss systemic, topical, intravitreal, transscleral, intrascleral, and suprachoroidal routes of drug administration and the underlying barriers and drug delivery principles in treating back of the eye diseases. Integral for any drug product development for the back of the eye are drug delivery systems. Chapters 9–16 discuss a variety of drug delivery systems, devices, and physical methods intended for drug delivery to the back of the eye. The delivery systems discussed include nanoparticles, microparticles, hydrogels, implants, and refillable devices. In addition, these chapters discuss physical approaches of drug delivery including ultrasmall microneedles for minimally invasive delivery and iontophoresis and electrophoresis for noninvasive drug and gene delivery. Further, as discussed in Chapters 17 and 18, even simple dosage forms such as drug solutions of macromolecules (e.g., Lucentis and Macugen) and drug suspensions of small molecules (e.g., Trivaris™ and Triescence™) are viable for prolonged back of the eye drug delivery.

No drug product enters the US market without receiving approval from the FDA. The FDA provides guidelines that are useful in ensuring the safety and efficacy of drug products. Chapter 19 describes these considerations. Key to assessing drug efficacy in the clinical setting is the identification and assessment of appropriate endpoints and biomarkers, as described in Chapter 19. Ongoing drug product development depends on the discovery of new diseases, targets and drug molecules. Chapters 21 and 22 present druggable targets and several therapeutic agents for treating back of the eye diseases.

This volume is intended for ophthalmic researchers, drug formulation scientists, drug delivery scientists, drug disposition scientists, and clinicians involved in designing and developing novel therapeutics for the back of the eye diseases. Further, this book will serve as a textbook for students in various disciplines including ophthalmology, pharmaceutical sciences, drug delivery, and biomedical engineering.

We are very thankful to Ms. Kristen Grompone for assisting us with the book preparation by communicating with the authors, coordinating manuscript submissions, and formatting the various chapters for publication. *Drug Product Development for the Back of the Eye* would not have been possible without the support of several authors, colleagues, and students in training. We are indebted to all those who made this volume possible.

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Drug Product Development for the Back of the Eye

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2011, XII, 592 p., Hardcover

ISBN: 978-1-4419-9919-1