INTRAOCULAR DRUG DELIVERY

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Preface

The development of drug treatments for diseases of the retina and back of the eye has been slow. Among the principal causes for this have been a failure of the pharmaceutical industry to appreciate the potential size of the market these diseases represent, a poor understanding of the disease processes themselves, and technical difficulty in delivering drugs to the back of the eye. There have been recent rapid advances in all three areas with many more changes likely to occur in the next decade.

Until the 1990s, very few drugs had ever been developed specifically for ophthalmology. Virtually all drugs used in ophthalmology had initially been developed for other applications and subsequently found to be useful in ophthalmology. One potential reason for this is economics. In 2001 it was estimated that it took over 12 years and cost over $800 million to develop and commercialize a new drug (1). For a company to undertake such an investment there must be a reasonable expectation that eventually sales of a new drug will, after allowing for development risk, at least recoupe its development costs. In 1996 the total world market for drugs for back-of-the-eye diseases was less than $500 million, providing little impetus to develop drugs for these conditions.

A major contributor to both the cost and the time it takes to develop a drug is the regulatory approval process. Following animal experiments, drugs enter limited clinical trials that often involve very few patients. These early studies, often called Phase I or Phase I/II trials, are generally designed to get a preliminary indication of safety and possibly efficacy while exposing as few subjects to the drug as possible. Once these studies have been successfully completed, a product can proceed to larger, Phase II trials. The goal of these larger trials, often involving 50 to 100 people, is to generate sufficient efficacy data to adequately power the next, Phase III, studies. It is these studies, sometimes called pivotal trials, that are designed to provide sufficient data to satisfy the regulatory agencies that a product is both safe and effective. Data collected in Phase II is generally used to ensure pivotal studies are appropriately designed and have sufficient statistical power to meet these objectives. These larger trials involve hundreds to thousands of patients. In clinical trials of an agent to treat a previously untreated disease it can be difficult to decide on the primary clinical trial endpoint to demonstrate drug efficacy. This is particularly true for diseases that are slowly progressing, where a clinically significant progression of the disease can take years. Any drug therapy designed to slow down the progression of such a disease is likely to require very long term clinical trials, increasing the time, the cost and the risk of developing a drug. Diseases in this group include diabetic retinopathy, neovascular and non-neovascular age-related macular degeneration, retinitis pigmentosa and

others. For a company developing a drug to treat these conditions, while risks from competitors are always present, they become magnified in the face of very long-term and expensive clinical trials. As a trial progresses, science advances and a competitor may develop a better drug or a more creative way through the regulatory system.

The difficulty of the Food and Drug Administration's (FDA's) task in approving drugs, especially for previously untreated diseases, should not be underestimated. Considerable pressure is exerted on the FDA to both approve drugs quickly and to ensure drugs meet the appropriate standards of safety and efficacy. The FDA is in a difficult position. If after approval significant side effects are encountered, the FDA is likely deemed to be at fault. On the other hand, if a drug is not approved quickly, the FDA is likely deemed to be at fault. The voices decrying the "glacial" pace of drug approval are often the same ones decrying the "cavalier attitude" of the FDA should a drug be withdrawn. Despite these pressures, the FDA can move extremely quickly to approve new drug treatments. Although it takes an average of 12 years for a drug to be developed, Vitrasert®, a sustained release delivery device to treat AIDS associated cytomegalovirus retinitis, progressed from in vitro tests to FDA approval in eight years. The total development time for Rertisert®, which recently became the first drug treatment approved for uveitis, was seven years. Both of these products were supported initially by grants from the National Eye Institute and without such support, the industry has rarely funded the development of such high-risk programs. For major pharmaceutical companies the risks of developing drugs for well understood diseases are high enough. Add to these risks an unknown market size, unfamiliar regulatory approval process, new drug delivery requirements and novel pharmacological drug targets, and the process becomes truly daunting. "Big Pharma" has not perceived the opthalmic marketplace as large enough to support a fully-fledged development effort. Pharmaceutical development has instead been largely limited to smaller, so-called "specialty" pharmaceutical companies.

A turning point in ophthalmology came with the approval of Latanaprost, a prostaglandin analogue. This molecule was developed specifically for glaucoma and has been commercially extremely successful, generating over $1 billion per year in sales in 2003 (2). This appears to have triggered the realization that ophthalmology has the potential to support billion dollar products and has lead to an increased focus on the area by the pharmaceutical industry.

In recent years there has been a dramatic increase in the understanding of the pathologies of ocular diseases and, perhaps not coincidentally, many new therapeutic candidates and pharmacological treatments. Unlike such mature fields as hypertension, there is as yet no clear consensus of the pharmacological targets best hit to generate an optimal therapeutic response. Not only are there now a large number of drugs under development but there are also a large number of different classes of drugs in development. Into the mix of increased commercial focus and rapidly advancing biology there is also the rapidly evolving field of drug delivery for the posterior segment of the eye. This state of high flux is exemplified by the three treatments for wet age-related macular degeneration that are either approved or awaiting approval. The first approved, Visudyne®, is an intravenous injection followed by an ocular laser to activate the drug in the eye. In 2005 it was followed by Macugen®, a vascular endothelial growth factor (VEGF) inhibitor, given by intravitreal injections every six weeks. Retaane™ is pending approval and is an angiostatic steroid given as a peri-ocular injection every six months. All three of these treatments have completely different modes of action and completely different means of administration.

This book is a snap shot in time. In it the contributors have attempted to describe some of the parameters influencing drug delivery and some of the attempts made, with varying degrees of success, to achieve therapeutic drug concentrations in the posterior of the eye. Also described are disease states of the back of the eye, some of which, like wet age-related macular degeneration, affect many people. Following the approval of Visudyne and Macugen, one could expect rapid changes in clinical management of these diseases. Other conditions, like retinitis pigmentosa, are very slowly progressing (making the design of clinical trials extremely difficult) or else affect only a small number of people, such as proliferative vitreoretinopathy (PVR). For these conditions there is as yet no precedent with the FDA for what constitutes an approvable drug. Progress in the management of such conditions is unfortunately likely to be much slower.

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