Chapter 1
Introduction to Muscular Dystrophy

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Introduction

The proteins and structures of certain processes associated with muscular dystrophy (MD) are beginning to be elucidated by scientists based on recent advances in our understanding of genetics. MD is a group of diseases that are clinically manifested in patients as progressive muscle weakness with associated loss of mobility, agility, and body movements as a result of defects in genes for the production of muscle proteins that result in the death of muscle cells and tissue.

With these scientific advances, the number of potential pharmaceutical targets has increased, resulting in heightened interest in investment, partnership, and collaboration. For example, GlaxoSmithKline (GSK) recently announced its first discovery partnership with academia, with the Fred Hutchinson Cancer Center for the treatment of FSHD [1].

In addition, many companies pursing potential treatments for MD have advanced to the Phase II and Phase III stage of clinical drug development, and one product from PCT Therapeutics may be fully approved in 2015.

This advancement from PCT Therapeutics would be the first drug approved for the treatment of the Duchenne and Becker forms of muscular dystrophy (DMD and BMD), which are genetic disorders that develop primarily in boys. They are caused by different mutations in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. Loss of dystrophin causes muscle fragility that leads to weakness and loss of walking ability during the childhood and teen years. Ataluren (to be marketed as Translarna™) is an orally delivered drug intended to overcome the effects of a specific type of mutation, called a nonsense mutation,

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which is the cause of DMD and BMD in approximately 10–15% of individuals with the disease [2]. A nonsense mutation is an abnormality in a sequence of DNA that results in a truncated, incomplete, and usually nonfunctional protein product.

To address the best way to study these potential treatments, the International Conference on Harmonization (ICH) communities responded by issuing limited draft guidance in Europe. The situation has similarities to that for biosimilars, where the European Union is ahead of the U.S. with regard to specific regulatory guidance. The European Medicines Agency (EMA) issued a concept paper in 2011 and, in early 2013, draft guidance for treatments related to DMD (and BMD). The U.S., on the other hand, appears to be relying on programs already in place to address the issues related to the potential treatment of MD. In 2013, when the U.S. Food and Drug Administration (FDA) addressed concerns from patient advocacy groups such as the Muscular Dystrophy Association (MDA), it cited existing programs to address the lack of specific MD regulatory guidance in the U.S. Programs specifically discussed included Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval and Priority Review [3].

This book provides an overview of MD with a focus on facioscapulohumeral MD (FSHD) in Chapter 3 and DMD and BMD in Chapter 4. Other forms of MD are presented and discussed, but not in as much detail, in Chapter 5. Later chapters, such as Chapter 11, examine some of the complex features that have made treatments for this group of diseases elusive. Chapter 10 provides an overview of the budding regulatory landscape for the treatment of MD in the EU and, finally, argues for more-detailed FDA guidance for each type of MD.

Lilleen Walters, who recently testified at a Congressional Briefing to reauthorize the Muscular Dystrophy CARE Act, said, “We must continue. If not us, then who? And if not now, then when? I believe that together, it’s time to do something. With reauthorization and modest investments, we can restore a lot of smiles to a lot of people.” It is important to note that Lilleen and her son, Collin, both have FSHD [4].

Additional Support for Patients and Families with MD

Advocacy groups are discussed in greater detail in Chapter 13, titled, “U.S. Patient Advocacy Groups”; however, it is important to recognize that, as my father, Raymond G. Huml, Jr., used to say, that “each person is comprised of body, mind and *spirit*.”

Indeed, in the June 25, 2014 letter from Pat Furlong to the FDA from the Parent Project Muscular Dystrophy, it is mentioned that each family, each parent of a child with DMD, has a different story to tell about their child’s lifetime progressive loss of function, loss of independence, and dependence on family and the extraordinary burden—physically, financially, emotionally, and *spiritually*—that DMD places upon the caregiver and family [5].

When I led a group discussion of parents of children with FSHD at FSH Society’s 2014 Biennial International Network Meeting in Boston, MA, several participants,

including myself, cited their spiritual beliefs as providing comfort and a more hopeful perspective related to a diagnosis of FSHD.

Based on my opinion, all resources should be employed to support and encourage the MD patient and their family, including communities found within churches, synagogues, and other places of worship. It can be comforting to know that a group is praying for an afflicted family member and help/assistance can be as practical as obtaining a meal at a difficult time or assistance related to the healthcare needs of a family with a member afflicted with MD.

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