

Executive Summary

The first cytokine-based therapies, Schering-Plough's Intron A (interferon alfa-2b) and Roche's Roferon-A (interferon alfa-2a, recombinant) to reach the market were approved by the FDA 25 years ago. Since that time, numerous cytokine-based therapies and inhibitors of cytokines and their receptors have reached the market, and several of these products have been blockbusters with over \$1 billion in annual sales. These include interferon alpha (IFN-alpha), interferon beta (IFN-beta), tumor necrosis factor alpha (TNF-alpha) inhibitors, erythropoietin (EPO) and erythropoietin-stimulating agents (ESAs), and granulocyte-colony stimulating factor (G-CSF). These are all established markets, but there are many new opportunities that pharmaceutical companies are pursuing. Emerging new cytokine-based therapies and inhibitors of cytokines and their receptors represent attractive markets that have become highly competitive.

Cytokines are a large, diverse group of extracellular proteins that are produced by immune system cells, and that act by binding to cytokine receptors on the targeted cells, thus starting a signaling cascade within those cells. This report focuses on cytokines including cytokine-based therapies and inhibitors that are on the market today, plus emerging new therapies.

Cytokines are extracellular signaling proteins that are produced by cells of the immune system and that mediate the immune response, either inducing

or suppressing an immune response. There are a large number of different cytokines that affect diverse populations of cells. Chapter 1 provides an overview of the field of cytokines. This is a complex field. Cytokines are pleiotropic, meaning that a single gene (or cytokine) can have more than one effect, affecting multiple different biological properties or phenotypic traits. In addition, the classification of cytokines is complex and can be confusing, and different systems may be used for this classification. Another factor contributing to the challenge of classifying and discussing cytokines is that some cytokines have multiple different names. Different ways to classify cytokines are discussed in Chapter 1. One approach is to classify cytokines into groups such as interferons, interleukins, the tumor necrosis factor family of cytokines, hematopoietic growth factors, and chemokines. This is the approach that is followed in this report, and each of these groups of cytokines is discussed briefly in the first chapter of the report.

Chapter 2 discusses approved cytokine therapies that are available on the market today. This chapter also discusses approved therapies that block interactions of cytokines and their receptors, and/or that block the activities/effects of cytokines. This discussion includes activities to expand approved indications and markets for cytokines and cytokine inhibitors already on the market, when those activities are occurring. A table of cytokine therapies and inhibitors that are on the market today is

included. Some early biosimilars are included in this table.

The pipeline of cytokine-based therapies is discussed in Chapters 3 and 4. Chapter 3 discusses selected emerging cytokine therapies, companies developing these therapies, the targeted indications, clinical progress or data (if available), and also issues or hurdles some specific emerging therapies may be facing. Tables of emerging cytokine therapies accompany this chapter, and the more advanced emerging therapies (later-stage clinical trials or submitted for approval) are discussed in the report.

Chapter 4 also discusses emerging therapies, but this chapter focuses on potential new therapies block cytokines or cytokine receptors, thus blocking the interaction of cytokines and cytokine receptors and therefore their activity. Again, this discussion includes information about targeted indications, clinical progress or data (if available), and also issues or hurdles some specific emerging therapies may be facing. Also, tables of emerging cytokine inhibitors accompany this chapter, and the more advanced emerging therapies (later-stage clinical trials or submitted for approval) are discussed in the report.

The long tables and discussion in Chapters 3 and 4 of the report show both the high level of interest in this field, and the high level of competition. Chapter 5 discusses some of the business and strategic considerations a company in this market should be aware of. This includes information on the current market for cytokines and cytokine inhibitors, including current sales of major products, plus brief discussions of the current and potential markets for emerging cytokines and emerging inhibitors of cytokines and cytokine receptors. These current and emerging therapies can potentially be used over a wide spectrum of different diseases and conditions. In addition, market trends, major challenges and hurdles, and other strategic considerations/issues are discussed. The final chapter (Chapter 6) of this report includes interviews with experts in the field of cytokines.