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Green Chemistry Strategies for Drug Discovery

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Preface

Green Chemistry Strategies for Drug Discovery is authored largely by veterans of the pharmaceutical industry, primarily in discovery, to address the incorporation of green chemistry principles into the fast-paced environment of drug discovery. The purpose of the book is to provide actionable strategies, case studies, and tools as a practical guide for both academic and industrial laboratories wanting to know how to start introducing greener techniques and, importantly, where to channel efforts for greatest return on investment. Recognizing that the incorporation of green chemistry into drug discovery is perhaps hindered most by resistance to cultural change, many of the examples provided are aimed at achieving incremental improvements that lead to the largest positive outcomes. As such, we anticipate and hope that, in the future, the actions recommended in this book will become routine and there will be a readiness to incorporate innovative technologies and tackle new challenges aimed at making our science more sustainable.

This book acts as a resource that could be utilized in its entirety or as a reference by topic area. In addition to expected subjects such as reaction optimization, high-throughput screening, analysis, purification, and solvent selection, the book addresses burgeoning fields such as continuous processing in drug discovery and green chemistry in biological drug discovery. Chapters also provide unique perspectives on green chemistry as it relates to patent protection and the electronic lab notebook, as well as the business case for the incorporation of green chemistry specifically in the drug discovery phase of pharmaceutical research. The majority of chapters are written by authors with experience in the pharmaceutical industry who can speak from an informed position, not only about what should be done, but what in fact has been accomplished. All authors represent a wealth of experience in the chosen subject area, and we greatly appreciate their willingness to share their expertise in this book.
We would like to especially thank Dr Berkeley “Buzz” Cue, Jr for his invaluable insight, perspective, and time to share his expertise with us. As a silent partner throughout this process, he also knew when encouragement would be more effective than critique. He has directly and indirectly influenced a significant transition in the sustainability of the pharmaceutical industry, and we are honored to have his guidance and friendship.

Finally, we would like to thank our families for supporting us through the duration of this project, which took more time and focus away from the most important things in life. During the development of this book, we experienced the death of several close family members, but also the birth of a new generation. We know those who have passed would have been proud of this accomplishment, and are rewarded by knowing the book enables a more sustainable future for generations to come.

Emily A. Peterson and Julie B. Manley
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CHAPTER 1

Introduction: The Five Ws of Pharmaceutical Green Chemistry

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1.1 Introduction

Louis Pasteur said, “Chance favors the prepared mind.” This chapter is designed to prepare the reader with the foundation upon which to build green chemistry into the business of drug discovery. Understanding green chemistry and its importance is a starting point, and being able to communicate it to the target audience is a necessity. By reviewing pharmaceutical green chemistry in the context of the essential journalism questions nicknamed the Five Ws (What? Why? Who? Where? When?), this chapter will provide an intentionally succinct perspective to act as the infrastructure for the invaluable chapters to follow. The Five Ws will prepare the reader to integrate green chemistry into drug discovery, and make successful integration more seamless and effective.

1.2 What is Green Chemistry?

First and foremost, green chemistry is chemistry, the scientific discipline of arranging molecules to create new materials and products; yet its focus is on the intentional integration of source and hazard reduction into the design of...
matter. By focusing on the design of materials at the molecular level, innovations are more efficient, cost-effective, safer, and environmentally preferable. Historically, environmental benefits were a side effect of optimizing efficiency and minimizing cost. Green chemistry turns that notion on its head and says that by intentionally designing a more sustainable process, the business needs will be met and even exceeded.

Green chemistry is commonly defined as the design of chemical processes and products to minimize the use and/or generation of hazardous materials.\(^1\) It is further clarified by a set of principles intended to provide a cohesive framework for the design of chemicals with reduced intrinsic hazard. The 12 principles begin with the recognition that it is more efficient to prevent waste from being generated in the first place than to treat it later (Principle 1). It is also more cost-effective to do so; the materials being purchased would be consumed rather than incurring a second cost on the same material for disposal. The principles address all aspects of the chemical lifecycle from the selection of safer materials (Principle 5 and Principle 12), renewably sourced where feasible (Principle 7), and their efficient use in the process (Principle 2). In the design of the chemistry, the principles emphasize the use of less hazardous chemical syntheses (Principle 3), reducing the need for derivatives (Principle 8), using catalysis where possible (Principle 9), incorporating real-time process monitoring (Principle 11), and minimizing energy use by considering ambient conditions when feasible (Principle 6). The principles also address end user considerations including designing the product to be effective while minimizing toxicity (Principle 4). Finally, in consideration of the end of the product life, the principles address the need to design for safe degradation in the environment (Principle 10). While some of these principles may not seem relevant to the drug discovery setting, decisions made in discovery can ultimately have a significant impact on the marketed product. The following chapters are intended to provide the reader with a more thorough understanding of their practical implementation in drug discovery.

For the current purposes, it is important to recognize the implicit challenge with implementing the 12 Principles in their entirety in any one process, and to appreciate this challenge not as a hindrance, but as an opportunity to continue to innovate.\(^2\) Even technologies recognized with the US Presidential Green Chemistry Challenge Award rarely, if ever, meet all 12 principles at any one time. Similarly, a process recognized as an effective implementation of green chemistry could also be further improved as evidenced by Merck’s sitagliptin, the active ingredient in Januvia™, being recognized in both 2006 and 2010 (with Codexis) with the Presidential Green Chemistry Challenge Award.\(^3\) The principles are a framework upon which to design, and to make informed decisions when a trade off between principles is inevitably needed.

One could argue that green chemistry is less a scientific field than it is specification for performance characteristics. Green chemistry describes how to incorporate design for the environment into current scientific methods. In 2005, metathesis was recognized with the Nobel Prize in Chemistry as a “great step forward for green chemistry”.\(^4\) The technology
received the highest honor globally in chemistry, not an environmental award, not a green chemistry award. Green chemistry is about doing chemistry more efficiently, safer, and more cost-effectively than it is now. Medicinal chemists, process chemists, analytical chemists, biochemists, and so on are not green chemists; they are scientists in their respective disciplines doing green chemistry. Job descriptions are not written to hire a green chemist per se; they seek qualified candidates able to perform the essential job functions. Arguably, knowledge of green chemistry, in addition to the targeted education and experience, assures the person is capable of utilizing his or her expertise to design and synthesize medicines efficiently, while minimizing cost and environmental impact, thereby meeting the short- and long-term goals of the company. Green chemistry is not a scientific field unto itself; it is the intentional integration of source and hazard reduction into chemistry. Paul Anastas, one of the fathers of green chemistry, has himself even been quoted, “I always say that we will know when green chemistry was successful when the term green chemistry goes away because that is simply the way that we always do chemistry.”

### 1.3 Why Should the Pharmaceutical Industry Incorporate Green Chemistry?

Sustainability, defined as meeting the needs of today without compromising the ability of future generations to meet their needs, was once a more commonly used vocabulary word for long-term financial stability than environmental stewardship. For the past 30 years, stability is not a term many would use to describe the pharmaceutical industry. Mergers and acquisitions have reduced what was once 110 companies to about 30 companies today, and that number is continually changing even as this book is being published. Figure 1.1 illustrates the history of AstraZeneca and Pfizer as examples to demonstrate the effect of mergers and acquisitions. At the time of writing, these two companies were engaged in communications for a possible merger.

R&D spending has been on the rise with approximately $51.1 billion spent in 2013, as compared to half that amount in 2000, and $1.2B in 1980, yet only two of ten marketed drugs return revenues that match or exceed the R&D costs. Restructuring has become the norm to manage these challenges. Whether it is outsourcing R&D or production, or spinning off companies like the Abbott surprising spin off of the R&D segment resulting in the creation of AbbVie, companies are downsizing and decreasing R&D spending throughout the industry. Lilly projected R&D spending to decrease 15–20% and Merck reduced headcount by 20% in 2013–2014 and minimized risk by acquiring experimental drugs. Companies need to do more with less, and green chemistry provides more for less. It is well established that the pharmaceutical industry generates a substantial amount of waste per kilogram of active pharmaceutical ingredient produced. Estimates indicate an average of over 100 kg material is used per kg
product produced (and even in the thousands for pre-clinical processes). With green chemistry, this has been shown to decrease to \( \sim 20 \) kg and even as low as single digits for some commercial processes. By utilizing the 12 principles, materials are used more efficiently, generating less waste and fewer hazards, lowering the standard cost for an active pharmaceutical ingredient. The use of green chemistry principles in drug discovery results in a faster production cycle time, which creates a competitive advantage.

Chemistry and innovation are the core of the pharmaceutical business. Bringing these together to discover and develop safe and effective medicines to help improve lives of patients is the objective. Achieving this goal cost-effectively with minimal environmental impact is the requirement. Green chemistry is the mechanism to meet these needs; it is an innovative, non-regulatory, economically driven approach toward sustainability:

\[ \text{“The core of what we do here is to define transformative medicine that will help the patient. The goal is doing chemistry that gives equal or better results and in a way that benefits the environment.”} \]

– Bruce Roth, Vice President, Drug Discovery, Genentech