COMBINATORIAL COMPOUNDS AND DRUG DISCOVERY

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1 INTRODUCTION

1.1 Overview

What Is a Drug? The U.S. Food and Drug Administration (FDA) defines a drug as: "(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)" [http://www.fda.gov/opacom/laws/fdcact/fdcact1.htm, Chapter II—Definitions, (g)(1)].

While this rather broad definition serves well for regulatory purposes for this chapter, the term *drug* must be narrowed to that more appropriate to the disciplines of pharmacology, pharmacy, and medicine. In this context, we will define a "drug" as a specific chemical species able to cause specific changes in the functioning of living things. More specifically, we will further narrow the definition to relatively small (<1500 Da) organic and occasionally inorganic compounds. This narrowed definition is not meant to indicate that the many macromolecular agents such as polyclonal or monoclonal antibodies or enzymes are of less value therapeutically, but merely recognizes the great difference between macromolecules and smaller discrete organic or inorganic molecules.

Pharmacokinetics, ADME, and Drug Properties Drugs, essentially by definition, are chemicals that bring about specific, often very specific and very potent, biological responses in their target organisms. However, it is insufficient for a chemical to be either potent or specific. Drugs must have other properties. When a drug is administered, it will follow a reasonably predictable course of ***a****bsorption* into the body, ***d****istribution* throughout the body, possible enzymatic ***m****etabolism* of the drug, and ultimate ***e****xcretion* (ADME). These processes, together with drug ***t****oxicity*, constitute the common pharmaceutical acronym, *PK/ADMET*, with PK standing for *pharmacokinetics*, which is to say the time course of a drug into, through, and eventually out of the body; it is what the body does to the drug (versus *pharmacodynamics*, which is what the drug does to the body).

Polarity and Drug Properties Pharmaceutical companies require certain properties of the drugs they discover, develop, and manufacture. Most importantly, drugs must be safe and effective. This is a trade-off. For some life-threatening diseases such as cancer or an acute serious infection, it is more important that a drug be effective than safe. On the other hand, drugs used very widely such as over-the-counter pain relievers or drugs taken regularly over years or decades for chronic conditions such as hypertension or osteoporosis are held to a much higher standard of safety.

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