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Alternate Methods for Assessing Absorption, Metabolism, and Routes of Elimination

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1. INTRODUCTION

This chapter will focus on the remarkable changes that have occurred during the past 10 years in our ability to evaluate many compounds simultaneously with respect to their pharmaceutical (drug-like) properties, including intestinal absorption, first-pass metabolism, and elimination. The majority of these advancements have applications at the interface between discovery and pre-clinical development, during which accurate and timely information can improve the quality of development candidates and reduce the risk of subsequent, costly failures in pre-clinical and clinical testing. Many of the alternate methods discussed herein are based on methods used for many years during pre-clinical testing. In the past, lead compounds were selected for development on the basis of pharmacological potency and efficacy in animal models, because a certain level of potency is pre-requisite to selecting a lead compound or series and, as potency increases, more delivery routes become reasonable options. Unfortunately, selecting for high potency often selects out favorable delivery properties (e.g., solubility and permeability). Historically, this strategy has failed to reliably identify potent ligands that were also well tolerated, efficacious medicines. During the last two decades, there has been a marked increase in the demand for new drugs exhibiting