CLINICAL TRIALS AND TRANSLATIONAL MEDICINE COMMENTARIES

Influence of the Compound Selection Process on the Performance of Human Clearance Prediction Methods

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ABSTRACT: This is a commentary on the series of five manuscripts written as part of the Pharmaceutical Research and Manufacturers of America Clinical and Preclinical Development Committee initiative on predictive models of human pharmacokinetics (PK). In particular, we wish to comment on the third paper in the series, which describes the performance of prediction methods of human clearance (CL). Human CL prediction methods described in the third manuscript are fundamental to the work presented in manuscripts four and five on the prediction of human PK profiles. In this commentary, we examine the influence of the compound selection process by performing a probability analysis and examining the CL properties of compounds that are selected using an idealized drug discovery screening process focused on PK optimization. The results of the analysis suggest that the selection of screening species can influence the performance of various predictive models of human CL. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:509–515, 2012

Keywords: allometry; interspecies scaling; *in vitro/in vivo* correlations (IVIVC); pharmacokinetics; human liver microsomes; clearance; hepatic clearance; preclinical pharmacokinetics

INTRODUCTION

We read with great interest the series of manuscripts describing the work performed by the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical and Preclinical Development Committee (CPDC) initiative on predictive models of human pharmacokinetics (PK).[1–5] These manuscripts describe a concerted effort by the pharmaceutical industry to assess the performance of various human PK prediction models in a blinded manner using compounds with properties more reflective of compounds currently being discovered and developed as medicines. The methods used in these manuscripts encompass most of the latest published methods of human PK prediction and, as such, this series of manuscripts was comprehensive. Despite the thoroughness of the analysis, we would like to highlight the influence of the compound selection process on the performance of human PK prediction methods, which is not addressed in these or other manuscripts. In particular, we wish to comment on the influence of the compound selection process on the PK parameter, clearance (CL). Human CL prediction methods are assessed in the third manuscript of the series[3] and are fundamental to work presented in manuscripts four[4] and five[5] on the prediction of human PK profiles.

The compound selection process inherently introduces biases to compound properties. The article by Kola and Landis[6] in *Nature Reviews Drug Discovery* shows the reduction of failures due to poor PK from the period 1991 to 2000. This reduction in failures can be attributed to the earlier optimization of PK in drug discovery utilizing both *in vitro* and preclinical *in vivo* PK models. In modern day drug discovery, the selection of compounds with adequate PK often utilizes *in vitro* methods such as metabolic stability studies in human liver microsomes and/or hepatocytes coupled with *in vivo* studies in preclinical species. Rats and dogs often serve as the most common preclinical

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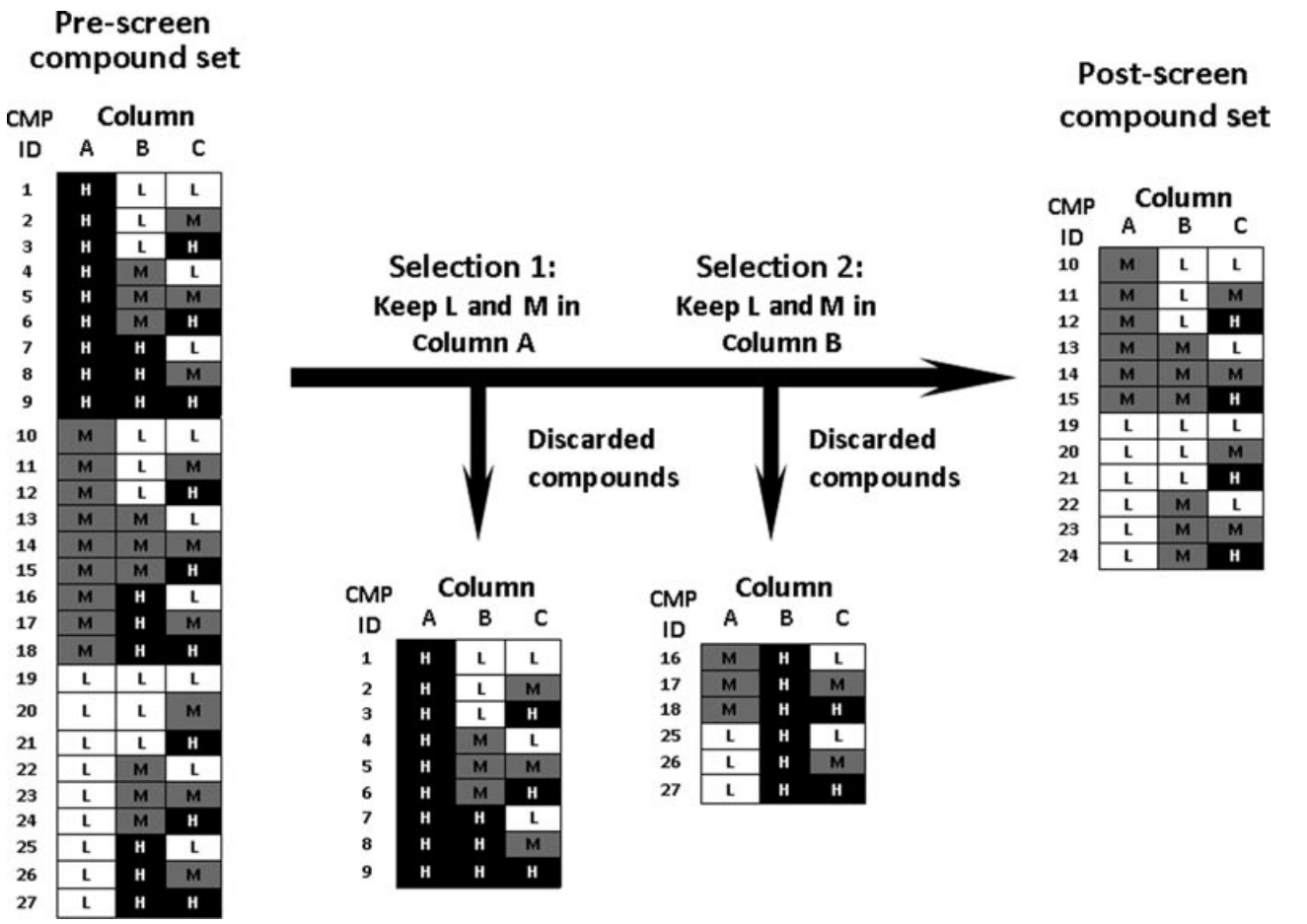

Figure 1. An illustration of selection bias on a set of 27 compounds (pre-screen compounds). The property of interest is assigned one of the three categories from highest to lowest as high (H), moderate (M), or low (L). Columns A, B, and C represent three sources of information for this property. Two sequential selections are made using information from columns A and B only. The post-screen compounds represent the compounds remaining following the two selections.

species used in PK optimization due to availability, cost, and likelihood to serve as toxicology species. The characteristics of the data used in the PhRMA analysis as well as recent pharmaceutical company-derived data sets published by others[7] attest to this because *in vivo* data is most abundant for rats and dogs. The selection of a drug candidate at the drug discovery phase involves the advancement of compounds down a screening "funnel." Advancement down the screening "funnel" is dependent on whether or not the compounds being evaluated meet the desired characteristics. Data from specific assays (e.g., metabolic stability in humans) are more abundant the earlier the assay is incorporated in the screening "funnel." Our objective in this commentary was not to critique the methods used in the comprehensive PhRMA analysis, but rather to raise awareness on the potential influence of the compound selection process on the properties of post-screen compounds and discuss potential implications to the performance of human prediction methods. We argue that the compound selection process creates an inherent bias that increases concordance between the preclinical and clinical properties being optimized.

INFLUENCE OF THE COMPOUND SELECTION PROCESS

Figure 1 provides a simple illustration of the influence of the compound selection process on the properties of post-screen compounds. We start off with a set of 27 compounds (pre-screen compounds) with a particular property that we wish to optimize. The property of interest can be categorized into three categories from highest to lowest as high (H), moderate (M), or low (L). Columns A, B, and C represent three sources from which we can derive information on this property. The initial 27 compounds represent all possible combinations of H, M, and L for columns A, B, and C. Two selections (selection 1 and 2) are made using columns