Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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I. INTRODUCTION

This document provides recommendations for sponsors of investigational new drugs (INDs) and applicants submitting new drug applications (NDAs) or biologics license applications (BLAs) on the use of exposure-response information in the development of drugs, including therapeutic biologics. It can be considered along with the International Conference on Harmonisation (ICH) E4 guidance on *Dose-Response Information to Support Drug Registration* and other pertinent guidances (see Appendix A).

This guidance describes (1) the uses of exposure-response studies in regulatory decision-making, (2) the important considerations in exposure-response study designs to ensure valid information, (3) the strategy for prospective planning and data analyses in the exposure-response modeling process, (4) the integration of assessment of exposure-response relationships into all phases of drug development, and (5) the format and content for reports of exposure-response studies.

This guidance is not intended to be a comprehensive listing of all of the situations where exposure-response relationships can play an important role, but it does provide a range of examples of where such information may be of value.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Exposure-Response Working Group under the Medical Policy Coordinating Committee, Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

II. BACKGROUND

Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known. There are some situations, generally involving a very well-tolerated drug with little dose-related toxicity, in which the drug can be used effectively and safely at a single dose well onto the plateau part of its exposure-response curve, with little adjustment for pharmacokinetic (PK) or other influences in individuals. In most situations, however, for more toxic drugs, clinical use is based on weighing the favorable and unfavorable effects at a particular dose. Sometimes with such drugs, the doses can be titrated to effect or tolerability. In most cases, however, it is important to develop information on population exposure-response relationships for favorable and unfavorable effects, and information on how, and whether, exposure can be adjusted for various subsets of the population.

Historically, drug developers have been relatively successful at establishing the relationship of dose to blood concentrations in various populations, thus providing a basis for adjustment of dosage for PK differences among demographic subgroups or subgroups with impaired elimination (e.g., hepatic or renal disease), assuming systemic concentration-response relationships are unaltered. Far less attention has been paid to establishing the relationship between blood concentrations and pharmacodynamic (PD) responses and possible differences among population subsets in these concentration-response (often called PK-PD) relationships. These can be critical, as illustrated by the different responses to angiotensin-converting enzyme (ACE) inhibitors in both effectiveness and safety between Black and Caucasian populations.

For the purposes of this guidance, we are using the broad term *exposure* to refer to dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., Cmax, Cmin, Css, AUC). Similarly, *response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (e.g., receptor occupancy) to a presumed mechanistic effect (e.g., ACE inhibition), to a potential or accepted *surrogate* (e.g., effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety. This exposure-response guidance focuses on human studies, but exposure-response information in animal pharmacology/toxicology studies is also a highly useful component of planning the drug development process (Peck 1994; Lesko 2000).

III. DRUG DEVELOPMENT AND REGULATORY APPLICATIONS

This section describes the potential uses of exposure-response relationships in drug development and regulatory decision-making. The examples are not intended to be all-inclusive, but rather to illustrate the value of a better understanding of exposure-response relationships. We recommend that sponsors refer to other ICH and FDA guidances for a discussion of the uses of exposure-response relationships (see Appendix A).

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