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0944 '02

May 31, 2002

To whom it may concern,

Please find enclosed comments from Cognigen Corporation regarding the "Draft Guidance for Industry Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications". This guidance was posted on April 1, 2002 under Docket Number: 02D-0095.

If you have any questions with respect to the enclosed comments, please contact me at (716) 633-3463 ext. 227 or grasela@cognigencorp.com.

Sincerely,

A handwritten signature in cursive script that reads "Ted Grasela".

Thaddeus Grasela, PharmD, PhD
President and CEO
Cognigen Corporation

TG: lp

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Comments

Guidance for Industry

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

Docket No. 02D-0095



Submitted to FDA

May 31, 2001

As pointed out in the guidance, exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. The development of analytical methodologies that facilitate the exploration of exposure-response relationships has been quite remarkable over the last decade. These methods provide the opportunity to assess exposures from patients enrolled in clinical trials and to relate this exposure information to efficacy and safety endpoints during the study. The guidance provides information regarding the potential uses of this information in regulatory decision-making and further points out the issues that must be addressed for the appropriate study and interpretation of these relationships.

There are two important obstacles in the performance and use of exposure-response information during drug development. The first of these concerns is the issue of generating knowledge necessary for decision-making in an efficient way. There are numerous examples of population pharmacokinetic/pharmacodynamic analyses that are presented at scientific meetings and published in scientific literature. The current inefficiencies in the generation of this knowledge, however, frequently result in considerable delays before this information is available and consequently precludes its use in real-time decision-making, both within the pharmaceutical company developmental team and within the regulatory agencies. The second obstacle relates to the difficulties that the current development environment has for incorporating knowledge into the decision-making process. Frequently, a strategy has been defined for development and the timelines required for the implementation of this strategy preclude

modification to the development program. This results in a certain rigidity, which does not allow for knowledge generated during the development process to modify the development strategy.

While individual development teams may have gained experience in the application of population PK/PD analyses and experienced the value it adds to the development process, the institutional memory for the value of these results can be of quite a short duration and the completion of a development program and constitution of a new team may result in a loss of appreciation for the benefit of these analyses. The draft Exposure-Response Guidance recently issued by the FDA provides an important opportunity to institutionalize the benefits of these analyses and holds out the promise of realizing an important return on investment for the efforts required to appropriately study and analyze exposure-response relationships.

In this context, important issues are raised by the current draft guidance. Early in the guidance (lines 66-68), the agency refers to the use of the broad term exposure to refer to dose, as well as various measures of acute or integrated drug exposure in plasma and other biological fluids (e.g., C_{max}, C_{min}, C_{ss}, AUC). In this one sentence, the agency is stating that dose-response relationships are equivalent to exposure-response relationships. This explicit definition of exposure at the beginning of the document could lead readers to interpret this document with the bias that dose-response analyses are always sufficient. This definition could also lead readers to miss the implied exclusion of dose from the exposure definition throughout most of Section III.B. For example, lines 172-176 state

“Exposure-response information can support the primary evidence of safety and/or efficacy. In some circumstances, exposure-response information can provide important insights that can allow a better understanding of the clinical trial data (e.g., in explaining a marginal result on the basis of knowledge of systemic concentration-response relationships and achieved concentrations).” This definition of exposure also leads to ambiguity in the definition of a well-controlled randomized trial for exposure-response analyses. Is a dose-randomized trial considered an adequate well-controlled trial for an AUC-response or Cmax-response analysis? Therefore, to enhance the clarity of the guidance, we believe that it is important to differentiate between dose-response and exposure-response relationships and their respective uses in the drug development process.

We also feel that in order to encourage the use of exposure-response analyses (in addition to dose-response), the guidance should expand upon the benefits that can be gained from exploratory analyses. The guidance clearly points out that “the more critical a role that exposure-response information is to play in the establishment of efficacy, the more critical it is that it be derived from an adequate and well-controlled study (see 21 CFR 314.126), whatever endpoints are studied.” The guidance also provides many examples of how these analyses can be used for improving decision-making during the drug development process, especially for determination of safety and efficacy. However, references to exploratory analyses (analysis of non-randomized data) are mixed with discussion of exposure-response analyses from adequate, well-controlled trials and only vague examples of how exploratory analyses can be used to improve decision-making are

mentioned (e.g., lines 130-135). Furthermore, the section beginning on line 349 (Concentration-Response Relationships: Two Approaches) leads the reader to the conclusion that very little useful information regarding exposure-response relationships can be gained outside the scope of a concentration-controlled trial. Our experience has been that exposure-response analyses (AUC, Cmax, etc.) conducted using data from dose-response studies provide remarkable insight over and above that provided through the dose-response relationship. These analyses provided a clearer understanding of the relationship between the pharmacodynamic endpoint and exposure, as well as the relationship between safety and exposure. Knowledge of these relationships has allowed wiser choices to be made regarding risk management during the planning of future clinical trials. These analyses can be especially helpful in selecting dosing regimens when the AUC-safety relationship or the AUC-efficacy relationship exhibits a rather steep ascent within a given dose level. The omission of examples demonstrating the importance of exploratory exposure-response analyses (dose and exposure) to the improvement of decision-making throughout the drug development process could lead to an attitude, although misguided, that only dose-response analyses have value during the early stages of drug development. This could have a negative impact on the gains that have been achieved thus far for incorporating exposure-response analyses into the drug development process.

Current interest in strategies to improve the efficiency and cost-effectiveness of drug development programs is high within the agency, as well as the industry. While there are numerous obstacles to the achievement of a more efficient process, this exposure-

response guidance provides an important opportunity to lend regulatory support to more efficient methodologies that, through an enhanced knowledge of the relationship between exposure and response, can lead to better labeling and safer use of medications by patients. In an effort to foster a safer and more efficient drug development process, it is important that the guidance be written to better demonstrate how exposure-response analyses (in addition to dose-response) can improve decision-making and streamline clinical trials throughout the development process.

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