INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

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Comments regarding *Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry; Availability August 2015.*

Guidance Document Section	Comment
General: Scope of Guidance	It is recommended that the Agency provide clarification if the scope of this guidance would encompass any clinical trial where there are limited numbers of patients available to study. For example, would the guidance apply to clinical trials with specific populations such as pediatric population or a particular ethnic group.
General: Risk Decisions	Given that rare diseases will require lower feasible sample sizes necessitating accepting more risk in decisions, we recommend the Agency articulate a policy providing greater clarity about how it will implement its "scientific flexibility" and particularly identify specific areas where it is and is not willing to accept more risk.
Line 363 Endpoint Selection	In selecting endpoints, statistical considerations such as information preservation and noise reduction may become more important criteria in small-sample cases. Although response and event-related endpoints may better identify clinically interpretable individual patient outcomes, continuous endpoints better preserve information and may permit evaluation with lower sample sizes. The balance between statistical feasibility and clinical interpretability may require different weighting in the rare disease case than in the typical case. "Ability to detect change", p. 9 line 363 et seq., may be intended to address this, but we suggest specifically addressing the statistical aspects including information loss and noise minimization.
Page 10	"Including several endpoints with different characteristics may improve the overall interpretability of the study results." When the choice of the primary endpoint poses problems, would the Agency consider performing the regulatory assessment based on consistent results of all relevant endpoints?
General: Type I error	For unmet medical needs and serious conditions without existing treatment, the Agency might want to consider relaxing significance (Type I error) requirements.
Page 13	"FDA recognizes that the investigation of potential drugs for the treatment of rare diseases is challenging, and study approaches used in

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	common diseases are not always feasible for rare diseases." In conditions with small populations, less conventional methodological approaches may increase the efficiency of the design and analysis (adaptive designs, randomization procedures, extrapolation, Bayesian approaches). Would the Agency consider such methodological approaches to be acceptable? Would the Agency consider the possibility to develop a framework for less commonly seen methodological approaches that are considered scientifically valid and reliable to support a Marketing Authorization to include in this Guidance?
General: Surrogate endpoints	For unmet medical needs and serious conditions without existing treatment, the Agency might want to consider greater reliance on surrogate endpoints, and reducing confirmation requirements if a surrogate endpoint is used for a preliminary approval. • As a practical matter, it is often very difficult to get patients to enroll/stay in a clinical trial to confirm a preliminary approval based on a surrogate endpoint. Difficulty in enrolling patients and risk that enrolled patients would crossover to study treatment once approved and commercially available tends to increase for rare diseases without existing adequate therapies, and once preliminary approval occurs confirmation may become infeasible. Accordingly, especially in the context of rare diseases with greater development difficulties and smaller potential markets, the Agency may want to consider steps to reduce the risk that potentially beneficial treatments may be trapped in a limbo where crossover due to perception of benefit prevents confirmation and approval. • The agency might want to consider use of historical controls for confirmation, e.g. whether use of the therapy substantially increases survival (etc.) compared to historical factors, in cases where a controlled confirmatory trial is impractical. • The agency might want to consider allowing adjustments for crossover in cases where widespread crossover is unavoidable.
General: Natural History	The Agency should consider that in order to avoid investigator bias during retrospective data collection in observational studies, it is recommended to blind patient identity.
Lines 477-482, Lines 491-497	The FDA position on sample size is somewhat contradictory and vague, as there is emphasis on adequate and well-controlled studies (lines 477-482). Then it also says (lines 491-497) that "There is no specific minimum number of patients that should be studied....". For an adequate and well-controlled study, one expects there to be a minimum number that satisfies the conditions of such a study. Clarification between these two sections is recommended.