European Federation of Statisticians in the Pharmaceutical Industry (EFSPI)

COMMENTS ON DRAFT FDA "Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics"

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GENERAL COMMENTS
In general this is a structured document, providing a well documented overview of the current status of adaptive designs.
Would it be possible to add the references in the text?
Some of the mentioned adaptive designs will shift from less to more “well-understood” as experience with these designs is accumulated as well as with published articles on methodology. This evolvement will require constant revisions in order for the guidance to be applicable. Is there any plan for this constant revision?

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE: III. DESCRIPTION OF AND MOTIVATION FOR ADAPTIVE DESIGNS

Line Number	Comment and Rationale	Proposed change (if applicable)
217-229	The category of the so called operational seamless studies (where data collected before the interim analysis is not used for the final analysis as opposed to inferential seamless designs) is not addressed. Yet operational seamless designs are totally different in nature (from both statistical and operational perspective) from inferential seamless designs and they do not raise any particular concerns since stage 1 (dose selection phase) data are not used for final inference. These designs would precisely be the most useful in "exploratory" and dose finding studies (phase 2), where FDA is the most encouraging for trying and expanding experience and knowledge.	

GUIDELINE SECTION TITLE: V. GENERALLY WELL-UNDERSTOOD ADAPTIVE DESIGNS WITH VALID APPROACHES TO IMPLEMENTATION		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
693-696	If the sample size decreases or increases after an SSRE depends on the (arbitrary) choice of pre-study sample size. A sponsor could avoid decreasing by having an optimistic pre-study sample size which anyway will be adjusted. The important recommendation that study resizing may be best applied later in the study, is already covered in e.g. 658-661.	
705-708	The example suggests that a blinded interim analysis could introduce bias. This seems to be inconsistent with the statements that this is not the case at other parts of the guidance.	
776-777	Although group sequential methods are well understood, estimation of treatment effects in a GS design is less straightforward. Additionally, overrunning may be an issue.	Provide some more guidance on these topics.
804-806	We do not agree that "compelling ethical concern" should generally be needed for early termination for efficacy in a group-sequential design (GSD). The guidance argues that early stopping leads to less safety data. This takes for granted that the maximal sample size in a GSD is the same or similar as the sample size in an alternative non-adaptive design. However, it is plausible that the sponsor chooses between a fixed sized trial of size N, and a GSD with interim analysis after N patients. The rational may e.g. be to increase the power for effect sizes somewhat smaller than originally expected (cf. unblinded sample size re-estimation). In this case, a GSD will always be at least as informative as the competing fixed design. It is more constructive if FDA in practical situations gives guidance on how much safety data that is needed. This amount may vary with the estimated effect as the net benefit-risk is central to a marketing authorization decision.	

GUIDELINE SECTION TITLE: VI. ADAPTIVE STUDY DESIGNS WHOSE PROPERTIES ARE LESS WELL UNDERSTOOD		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
980	The original Play-the-Winner design is limited to two treatments and immediate responses. Recent advances in the methodology of response-adaptive designs (or design with dynamic treatment allocation) are only very briefly touched upon. But they show several advantages including ethical.	Include the references Wei et al. (1978), Eisele (1994), Rosenberger et al. (2001), Ivanova (2003), Sun R. et al. (2006), Zhang LX et al. (2007), Lecoutre et al. (2008).
1023-1068	It is stated that using an adaptation of sample size late in the study is not advisable because a large percentage increase in sample size at that point is inefficient.	Clarify that too early adaptations may lead to imprecise interim estimates, while too late adaptations may be inefficient (for the reasons stated in the draft text). Suggest here also that calculations / simulations of the design properties are useful to guide the choice of adaptation time(s).
1076-1110	It is stated that only adaptive designs for which design adaptations are prospectively planned are addressed in this guidance. While pre-specification is certainly desirable it should be recognized that it is often not realistic to fully pre-specify the adaptation rules of e.g. a dose selection algorithm. This is especially important in the setting of exploratory studies. Moreover many key papers have been published over the last decade proposing adaptive designs that do not require prospectively planned adaptations while offering good statistical properties, which could be applied in exploratory studies.	Can it be clarified whether there is less requirement on pre-specification of details in exploratory studies? This could be done in Section IV.D.

GUIDELINE SECTION TITLE: VII. STATISTEICAL CONSIDERATIONS FOR LESS WELL-UNDERSTOOD ADAPTIVE DESIGN METHODS		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
1318	Allowing Bayesian predictive probabilities in decision making, but maintaining control in the frequentist sense suggests that a full Bayesian approach (i.e., applied to both decision making and analysis) is not recommended. Is this indeed the case?	
1341	Does this statement imply that adaptive designs — for which control of the type I error rate is only established using simulations — are unacceptable? This seems to be in contradiction with 'Computer simulations intended to characterize and quantify (…) impact on the Type I error' (lines 1518-1519).	Suggest refining text and adding that it may be difficult to simulate all possible scenarios under a complex null hypothesis, but that simulation is in principle a valid method of calculating the type I error provided that the null space is adequately covered and the simulation random error is accounted for.

GUIDELINE SECTION TITLE: IX. CONTENT OF AN ADAPTIVE DESIGN PROTOCOL		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
1539	'For each design evaluated (..)' suggests a reference to all alternative designs considered before deciding on the final adaptive design.	Suggest to change: If the chosen design is evaluated (..)