Document Title: **Draft Guidance for Industry Guidance on Adaptive Design Clinical Trials for Drugs and Biologics** [Docket No. FDA– 2010-D-0090]	**International Society for Clinical Biostatistics (ISCB) www.ISCB.info**	**Date: 21-May-2010**

Page/ Line No	**Comment (with rationale)**	**Proposed change**
General comments		
	EMA guidance already exists for "Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design" (CHMP/EWP/5872/03)	Please clarify differences and communalities
	Besides the immense work on reviewing there are also highly valuable general elements e.g. regarding DMC/DSMB, SAPs, bias identification etc which reach beyond ADCTs which render the document from a biostatistical point of view very thoughtful and inspiring.	ISCB commends the agency, all FDA centres involved, and all FDA scientists contributing to this guidance for having compiled a comprehensive document on the methodology of adaptive designs. The text has the capacity to set new standards not only for adaptive designs for clinical trials but also for the use of statistical methods in drug research and the society strongly recommends the implementation for improving good clinical practice, including good statistical practice. The guidance document is very welcome at this time, when the method of adaptive designs introduced for improving the efficiency of clinical trials reaching the age of 20 years (starting with the starting with the seminal work of Peter Bauer and his colleagues in the late 1980ies) is now increasingly used both in clinical trials sponsored by pharma industry as well as by academic institutes.
	The guidance needs a glossary beyond the part III, B where terms like results, outcomes, endpoints, study parameters or the terms like baseline patient characteristics, baseline study characteristics (L86) are described.	Provide a glossary and distinguish in the document explicitly between, patient data, study, and administrative data. This becomes in particular relevant in the discussion of interim analyses (L 150).

	The guidance introduces A&WC and Explanatory Studies as study types but uses at the same type also non-A&WC in overlap with Explanatory Studies. At the same time it is said that this notion is not compatible with that of Phase I-III or with that of confirmatory vs. non-confirmatory studies which may a source of confusion.	Clarify the notion of study types and guide the designers of clinical trials who from other guidance documents may be familiar with other conventional notions. Which study types are admissible for ADTCs as described in this guidance? Define the role of a trial with internal pilot study (which was actually one driving argument when ADCTs started to be developed by Bauer&Köhne) if there is any role of those in the concept of A&WC and Explanatory Studies dealt in this guidance For understanding the difference between the two types it could be helpful to distinguish whether in a development programm the A&WC is performed before or after an Explanatory Study.
	The guidance seems to argue against the application of of designs which have been introduced recently as so called "seamless designs" (see e.g. L 535) but is not explicit about that	Clarify whether "seamless designs" are covered by the guidance and, if yes, whether they are seen as non-well understood designs.
	The guidance does not elaborate on the steps performed during the conduct of a trial referring to an adaptive designs different form the steps caused by amendments which also have the aim to adapt the trial to arising issues. See e.g. L 631	Clarify the different types of adaptations originating from steps of an adaptive design and from stepwise amending the trial protocol- Give guidance when those two processes interact (e.g in population selection, change of baseline characteristics). This could be addressed in Section 1- 3- in chapter IV A. Check with the section L 630-634.
	The guidance does not address the problem of "overlap of patient event histories" when time-to event is an endpoint and the independence assumption of the log-rank/score statistic may be violated.	Elaborate more in time-to-event studies.
	Recommendations for study designs other than parallel group designs, e.g. cross-over studies would be useful	
	The draft guidance was reviewed by Quintiles personnel from biostatistics, regulatory and medical departments. A general comment from all reviewers is that the draft guidance is very thoughtful, comprehensive, and well written. Two reviewers noted that the guidance is very technical, and at times hard to follow for non-statisticians.	

	We request that inclusion of more references to articles written by PhRMA Adaptive Design, and Adaptive Design Dose-Ranging studies working groups.	
Specific comments		
L 23		We suggest replacing “include in the adaptive design” with “include in supportive documentation for the adaptive design”.
L 39		Please add after “if one exists,” the following “more accurate (e.g., higher precision)”.
L 43-51	The document distinguishes between familiar and less familiar approaches in drug development programs. Later in the guidance (V), the notion of well-understood designs is used for the ADCTs. The notion of familiar design methods is also used to characterize experienced use. This causes some confusion. As an example: Are group-sequential designs familiar or less familiar classified? Is there enough experience with them? Have all stakeholders understood them?	Clarify the use of terms characterizing ADCTs. Clarify the degree of novelty and complexity from which on a design is less familiar to whom (regulators, sponsors or statisticians). Note that in line 164 the term conventional study is used to denote a fixed sample size study. This add another term.
L 83	Does the guidance confine on trials with at least two arms where at least one arm is a control arm?	Provide a precise definition on the type of studies considered in this guidance document with respect to treatment arms compared.
L 99		We suggest replacing “analytic” with “analysis here and throughout this document, i.e., “statistical analysis plan”.
L 114	analytical methods	Distinguish between clinical analytical measurements (e.g. CT, sonography) and statistical analysis methods
Section III, B L 138	Clarify who is meant by ‘decision makers’ (line 159). Stipulating that by-group comparisons with identification of groups masked classes as an unblinded analysis is very strict and would lead the majority of trials to have unblinded analyses, if ‘decision-makers’ includes the data monitoring committee	
L 143	"Interim analysis, for purposes of this guidance, is any examination of the data obtained in a study while that study is still ongoing, and is not restricted to cases in which there are formal between-group comparisons." footnote3: "This definition is different from the definition in FDA’s International Conference on Harmonization (ICH) guidance, E9 Statistical Principles for Clinical Trials (ICH E9 guidance),"	Need the definition be different?
L 154	Blinded for whom?	It may be better to discuss and define blinding in a separate chapter later. There are indeed excellent sections later in the document where blinding is clearly addressed.
L 167	The term “bias” has been used somewhat loosely.	We suggest clarifying the terminology.

L 168 172	Increase of type I error is usually not source of bias in the statistical literature	Clarify the term bias in relation to type I error.
L 217	It would be useful if the FDA discusses its position on operationally seamless Phase IIb/III studies.	
L 257	In life-threatening disease, there is - in addition to the non-usefulness of stopping a suboptimal dose group - the requirement to stop a suboptimal dose group for ethical reason.	Differentiate between life-threatening and non-life-threatening disease.
Section IV, A.3 L 286	Is it really possible to keep detail of any adaptive choices from the investigators, in particular the Chief Investigator. This needs more clarity as to what is meant by 'adaptive choices'.	
L 402	"All plans for the conduct of the unblinded interim analysis, dissemination of interim results, study modification decisions (of any kind), and distribution of detailed knowledge of the decisions should be carefully considered and documented."	"All plans for the conduct of the unblinded interim analysis, dissemination of interim results, study modification decisions (of any kind), and distribution of detailed knowledge of the decisions 405 should be carefully considered and documented **in advance**."
L 412	The guidance makes here - and also at some other places- a very strong link between ADCTs and dose-response analysis, in contrast to the fact that many ADCTs have been developed for the comparison of treatment arms not defined via dose groups.	The guidance should distinguish between ADCTs for the comparison treatment arms defined by the categorization of therapies and ADCTs for the dose finding and the characterization of dose-response.
L 448-458	One concern with exploring study results between phases is that this may result in too much "data dredging" and allow for "unexpected aspects of the data". This could also cause bias if the phase A&WC study was planned with these unexpected data results in mind.	We suggest discussion in the document as there is a value in some pre-specifying goals/benchmarks even if there is ample time for exploring study results.
L 632	The guidance seems to suggest explanatory data analyses within an A&WC study. Note that such additional analyses would also apply before and after the implementation of amendments.	Clarify any additional role of explanatory studies and provide more information how an analysis as suggested in L 633 can be performed.
L 636	"post baseline data"	Clarify in a glossary

L 640	It is important to explain some risks associated with adjusting sample size based on blinded data in section V.B. An example is that a smaller number of events than expected can be observed due to better than expected treatment effect, even if the control rate is consistent with the assumed one. Reversely, if the control rate is higher than expected, the aggregate rate may be on target, while the treatment effect is lower than expected (but possibly still clinically meaningful). In this case, the sponsor may incorrectly decide not to adjust the sample size.	Please explain these risks in section V.B.
L 649	Power can change in both directions	"under- or overpowered"
L 655	"If this comparison suggests the actual event rate is well below the initial assumption, the study will be underpowered."	it could be overpowered if the expected proportion was 50% and the observed was 40%.
L 656	The statement depends on the way how effect size is defined. If an absolute difference of proportions is used as effect measure, that difference would be detected with a higher power al lower proportions.	Precise the effect size or write "can".
Section V, B (beginning line 663)	It is unlikely to be acceptable to funding bodies to not plan a specific study sample size and to just wait until the required number of events has occurred. This is not a practical approach to clinical trials.	
L 679	The guidance seems to assume that the ADCTs contains a non-active control . However, in many chronic and/or life-threatening diseases (e.g, cancer) a non-active control would be unethical.	Clarify the scope of the guidance in respect to application for trials for drugs for the treatment of life-threatening disease. See e.g. also L 928, L 1013- 1026
L 694	“Decreasing sample size is not advisable” Line 1047 states “Adaptive designs employing these methods should be used only for increases in sample size not decreases.”	Is it intended for the language in the two sections to be purposefully different, or should the message be more consistent?
L 840	"Adaptations in the Data Analysis Plan"	"Adaptations in the Statistical Analysis Plan"
L 843	"statistical analytic plan"	"statistical analysis plan"
Section V, E (beginning line 860)	It would be useful to note here that the proposed analysis for the primary outcome (and ideally all other outcomes) should always be specified in the analysis plan prior to looking at the data.	
Section VI,A (beginning line 954)	It is not clear here what would happen to the patients who are allocated to the treatment which is to be terminated therefore clarification would be useful.	

L 975	The term adaptive randomization has also been used for randomization scheme balancing for covariates.	Clarify " outcome dependent randomization" from that other type
L 980	The most commonly used term in literature is “response adaptive randomization”.	We suggest use of “response adaptive randomization”.
Section VI, G L 1023	Adaptations in non-inferiority studies: It would be useful to include guidance on whether an unblinded review is permissible in order to stop the study early (due to already demonstrating evidence of efficacy or else for futility).	
Section VI, C l 1023	Adaptation of sample size based on interim effect size estimates: The guidance recommends that only increases in sample size are appropriate when re-estimating the sample size at an interim analysis. However, if there is sufficient information at the interim analysis to provide a sufficiently stable estimate of the treatment effect, then would it be allowable to have a reduction in sample size (particularly if the initial estimate of variability/ response rate was based on a pilot study or data in the literature with fewer patients than at the interim review)? Otherwise, may be exposing more patients than required to treatment/control groups. It would also be useful to incorporate guidance as to the minimum number of patients or events that should be recruited / observed before a sample size reassessment can take place reliably.	
L1040	The guidance argues against the implementation of an adaptation late in the study because of a larger percentage increase in sample size at that point would be inefficient. That argument is questionable if not incorrect since the efficiency of that adaptation would depend on the increase of effects and on how efficiency is defined, in particular, however, on how the study will continue.	Delete the sentence.
L1059	"reasonable"	Secify" reasonable" or reformulate. "Statistically correct" is an option!
L1093	The guidance addresses a very complex issue when combining dose selection with patient population selection to be treated in one ADCT	Make clear that this is a non well understood area which needs more research.
L1105	"for all hypotheses "	"for all primary hypotheses"
L 1163	footnote6: "will publish soon."	"will be published soon."
L1186	Why can upcoming new information not also lead to changes of the non-inferiority margin? New information on toxicity could change the risk-benefit consideration and thereby the margin.	State the requirements for non-inferiority trials or exclude them from this guidance. Harmonize with the upcoming guidance on non-inferiority, anyway.

L 1260	"obtained"	"estimated". Refer to the different methods of combining p-values or the inverse normal methods-
L 1271pp	alpha-spending	Add ß-spending, see e.g the work of Hwang et al.
L 1307	Suggested text	endpoint occurrence or disease progression, and the postulated patient treatment adherence, withdrawal, or dropout
L 1309	Suggested text	for changing doses, ~~changing~~ exposures, responses, ~~durations,~~ and/or variability ~~in bioavailability~~
L 1357		Please insert “unplanned” between “any” and “design”
L 1389	within patient dose-escalation is a relevant issue in many phase I trials	Do mention within patient dose-escalation and clarify whether this is covered by this guidance. Better exclude!
L 1395	There is an intention in oncological phase I studies to rapidly increase doses for finding the highest tolerated dose in few steps, see e.g. the CRM method	Delete line 1395
L 1402	" to reach the middle or higher end"	"to reach the target level of efficiency and/or safety"
L 1446/7	We note that most adverse effects will indeed be able to be ameliorated in the context of adaptive study designs by employing safety monitoring with increased frequency, greater data scrutiny/”signal detection algorithms (or both); additionally, most of those adverse effects which may present challenges in the adaptive paradigm (e.g., those which are functions of “significant” length of time of ongoing threshold exposure, “significant” time post first threshold exposure, or are rare/idiosyncratic in nature) are already challenging to identify with safety monitoring techniques employed in “standard” designs, and by their nature are not generally able to be prospectively identified so as to employ the “alternative” safety measures noted (line 1447). This comment is offered both to confirm the potential additional inherent risk in any (expedited) adaptive design for the above (generally uncommon) safety concerns and to suggest that in some ways mitigation of such risk while embracing the expedited design are indeed mutually exclusive.	

L 1447-9	The aspect brought into the guidance at this place is in so far critical as it calls for the recruitment of patients for "sufficient safety" without asking for a thorough study plan. This raises an ethical issue not only because there is no hint to prospective planning but also because there is no distinction between life-threatening and non-life threatening disease. The case could be very different between treatment of cancer and treatment of headache.	Implement a distinction between life-threatening and non-life threatening disease and reformulate that section
L 1482	We suggest mentioning the Simulation Report as a supportive documentation required for complex adaptive designs; its scope, content, and timing.	
L 1502		We suggest replacing “models” with “rules”.
L 1503	"quantitative justifications for conclusions"	This term needs explanation. Better delete the last part of the sentence.
L 1515	It is also important to inform on the timely course of the study.	Ask for presentation of the time course and actions taken at checkpoints.
L 1554	"along with the statistical bias in the estimate"	" along with statistical methods for unbiased effect estimates"
L 1556	Type I error should be controlled at the study level, rather than at the individual stage level.	
L 1565	Inform on all parties, committees and persons and their being blinded or unblinded at the various stages and checkpoints of the study.	The documents -preferably already the study protocol should inform on all parties, committees and persons and their being blinded or unblinded at the various stages and checkpoints of the study.
L 1556	Type I error should be controlled at the study level, rather than at the individual stage level.	
L 1654 - 1675	Section X.C of the draft guidance states that Adaptive Design Trial Protocols may take advantage of Special Protocol Assessment (SPA) procedures, but because of the inherent difference between Adaptive Protocols and non-adaptive protocols, FDA’s advice is not binding and the time frames may be longer.	The FDA may consider this to be a separate category of protocol review, e.g., as used for Carcinogenicity Protocol and for Stability Protocol Assessments. This may also permit FDA to establish a different time frame for their review.
L 1795	It is the additional shift caused by the adaptation that matters	Distinguish between usual shift and additional shift.