Chapter 2
Regulatory Guidance Documents on Adaptive Designs: An Industry Perspective

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Abstract Adaptive designs have the potential to be a transformative methodology in clinical drug development, but acceptance by regulatory agencies is a prerequisite for their broader adoption and success, especially in the context of confirmatory studies. Both FDA and EMA have published guidance documents focusing on adaptive designs, which have been neither discouraging nor clearly supportive of the approach in their assessments and recommendations. As a result, the interpretation of the *regulatory position* on adaptive designs also has been mixed, with some citing the guidance documents as evidence that health authorities do not accept adaptive designs, while others mentioning the same documents as indication that regulators support their use in drug development, when properly planned, conducted, and analyzed. This chapter reviews and discusses the two main regulatory documents on adaptive designs issued by the time this book was published: the reflection paper by EMA (Reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plan (draft CHMP/EWP/2459/02, 23-Mar-2006), 2007) and the draft guidance by FDA (Adaptive design clinical trials for drug and biologics draft guidance, 2010). Reactions from the biopharmaceutical industry to both documents, collated by industry trade groups, are also presented and discussed.

Keywords FDA draft guidance • EMEA reflection paper • Well-understood and not well-understood adaptive designs • Operational bias • PhRMA Adaptive Designs Working Group

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2.1 Introduction

Adaptive designs (AD) have the potential to transform clinical drug development, as discussed and illustrated throughout this book. The very reason that makes AD attractive to drug developers, the opportunity to make pre-planned design and analysis modifications to an ongoing clinical trial, also raises understandable concerns from regulatory agencies (RA), especially when utilized in confirmatory studies. The ultimate success, or failure, of AD in the context of drug development hinges on their acceptance by RA around the world. This was recognized early on by industry groups advocating the broader use of AD in drug development, most notably the PhRMA Adaptive Designs Working Group (ADWG). Members of the ADWG engaged in early discussions on AD with RA in the USA (FDA), Europe (EMA), and Japan (PMDA), emphasizing the importance of guidance documents to provide a clear position with regard to regulatory acceptance, or not, of AD.

Two guidance documents focusing on AD were issued, at least in part, as a result of the advocacy efforts by industry groups: the EMEA reflection paper (EMEA/CHMP 2007) and the FDA draft guidance (FDA 2010). The former is a relatively short, high-level document, focusing almost entirely on confirmatory studies—neither encouraging, nor ruling out the use of AD, from a regulatory perspective. The FDA draft guidance is considerably more detailed, covering both exploratory and confirmatory studies (but with greater emphasis on the latter), and providing not only potential regulatory concerns about the use of AD but also recommendations on how to circumvent them in drug development practice. Although its overall tone is broadly supportive of adequately planned, executed, and analyzed AD, the FDA draft guidance has been interpreted by some in the biopharmaceutical industry as evidence that FDA does not favor the use of AD.

Both guidance documents elicited strong, mostly positive reactions from industry groups, who provided many comments and suggestions during the respective review periods. The EMA reflection paper incorporated some of the suggestions received during the consultation period (and provided responses to those which were not adopted) in the final version adopted by CHMP. The FDA draft guidance was yet to be revised and finalized at the time of publication of this book.

This chapter reviews both the EMA and FDA guidance documents on AD from an industry perspective. Section 2.2 describes the FDA draft guidance, discussing its impact on the biopharmaceutical industry. The EMA reflection paper is covered in Sect. 2.3, being contrasted to the FDA draft guidance. The industry perspective on both guidance documents and, more broadly, on the perceived regulatory position on AD are discussed in Sect. 2.4, with a focus on comments and recommendations issued over time by the ADWG.

2.2 US FDA Draft Guidance on Adaptive Designs

Even though the EMA reflection paper was issued prior to the FDA draft guidance, the latter is presented and discussed first in this chapter, as it has a considerably broader scope and has had more impact in industry than the former. The guidance document on AD was a PDUFA IV commitment of FDA, originally scheduled to be issued by October 2008 and finally published in March 2010. The inclusion of a guidance document on AD as part of the PDUFA IV negotiations was a clear indication of the importance that the biopharmaceutical industry placed on this methodology as a tool for modernizing and improving the efficiency of drug development, as a well as a recognition that regulatory guidance was a critical prerequisite for its successful utilization. The formation of the PhRMA ADWG in early 2005 also provided clear indication of the industry support for and interest in AD. The ADWG played a critical catalyzing role with regard to broad awareness, early adoption, and regulatory engagement on AD. The ADWG went on to publish a series of highly impactful white papers (Gallo et al. 2006; PhRMA 2006; Bornkamp et al. 2007; Antonijevic et al. 2010; Gallo et al. 2010; Pinheiro et al. 2010), to engage in productive discussions on AD with RA around the world (FDA, in particular), and to disseminate AD at scientific conferences. A good number of issues advocated by the ADWG made their way into the FDA draft guidance, but many were left out.

The overall tone of the FDA draft guidance is *encouraging of AD, but with caution*: the document states that FDA recognizes AD as having the potential to improve the efficiency and success rate of drug development, but raises some concerns about their use, mostly in the context of pivotal studies. It also acknowledges that the main appeal of AD is to allow pre-planned midway corrections to ongoing trials, revising design assumptions and research goals in light of observed data. Two main regulatory concerns are expressed early on and throughout the guidance: the potential for *Type I error rate inflation* and *operational bias* that could compromise study integrity and the validity/interpretability of the final results. The cautionary tone is pretty much consistent with regulatory guidance documents issued on other topics, but it was perceived by some in industry as an indication that FDA would be reluctant to accept AD, especially for confirmatory studies.

2.2.1 Description and Motivation for Adaptive Designs

The guidance defines AD as a clinical study that includes a prospectively planned opportunity for modification of one or more aspects of its design and hypotheses, based on analysis of data (usually interim data) from subjects in the study. This is consistent with other references on AD, including the ADWG Executive Summary (Gallo et al. 2006), which defines AD as *a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial*. By *prospectively* the guidance means before any unblinded data analysis is performed, but the recommendation

put forward in the guidance is that any adaptation be planned, described, and evaluated before the study protocol is finalized. In addition, the timing of any adaptations should be pre-specified. The adaptations can be based on blinded or unblinded data, and may or may not include statistical hypothesis testing. A number of potential study design modifications that can be implemented in an AD are listed in the guidance, including

- Study eligibility criteria
- Randomization procedure
- Treatment allocation (e.g., dose, schedule)
- Total sample size and/or study duration
- Concomitant medication
- Planned patient evaluation schedule
- Primary endpoint (e.g., single vs. composite)
- Secondary endpoints (selection and testing order)
- Analysis methods to evaluate endpoints

The two main types of adaptations discussed in the guidance are *treatment allocation* and *total sample size/study duration*. Some of those potential adaptations, like the *primary analysis method*, appear to be included in the guidance just for completeness as they are declared as *unlikely to be acceptable* from a regulatory perspective right after being listed.

FDA acknowledges the motivation for AD in the guidance, naming, in particular the improvement in knowledge efficiency compared to conventional (i.e., nonadaptive) study designs (same information faster and/or cheaper; or more information for the same investment and time). Additional potential advantages of AD also mentioned are the increased likelihood of success (via midtrial corrections), the reliable early termination via futility rules, and the improved understanding of treatment effects (e.g., better evaluation of dose–response profile or subgroup effects).

2.2.2 Study Types

The guidance differentiates between two types of studies for which AD can be considered: adequate and well-controlled (A&WC) effectiveness studies intended to support drug marketing and exploratory studies, which can be considered as the complement of A&WC studies. From the point of view of AD, the main difference between the two types of study is that for an A&WC study strict control of Type I error rate is paramount, while for exploratory studies it is less critical. The focus of the guidance is on AD in the context of A&WC, but AD in the context of exploratory studies are also discussed in the document.

From a methodological perspective, the main concern expressed in the guidance about the utilization of AD with an A&WC study is the potential inflation of Type I error rate, with possible bias in the estimation of treatment effects also being mentioned, but somewhat downplayed. It is acknowledged that statistical methods

have been developed to adequately control Type I error for a wide range of AD based on unblinded data (there is less of a concern about Type I error inflation when adaptations are based on blinded data), but it is emphasized that it is incumbent upon sponsors to demonstrate, preferably analytically, that the proposed statistical analysis methods will indeed control Type I error under the planned AD.

The other main concern related to AD in A&WC studies expressed in the guidance is harder to pin down and ensure control over: potential for operational bias due to leaking of unblinded results as the study is ongoing. If present, it could jeopardize the scientific validity of study, making results difficult to interpret and accept. Changes in patient population after an unblinded adaptation are cited as an example of operational bias associated with AD. Of course, changes in patient population during a clinical trial can, and do, also occur when no adaptations are used in the study. They may be the result, for example, of different regions/sites starting recruitment later in the trial. The recommendation, implicit in the guidance and expressed by FDA representatives at conferences and public meetings following the publication of the draft guidance, is that sponsors should ensure, and document, "squeaky clean" execution of AD to avoid any potential indication, real or perceived, that access to unblinded data during the study led to operational bias. Since the publication of the draft guidance, different vendors have developed commercial software to support the execution of AD that can be used to document the data access operational integrity of AD (see Chap. 8, on available software for AD).

The draft guidance explicitly encourages the use of AD in the context of exploratory studies, stating that they provide a natural framework for learning about dose–response, subgroup effects, etc. and have the potential to lead to substantial gains in knowledge efficiency. It is also mentioned that exploratory studies provide a natural framework for implementing and getting familiarity with unblinded adaptations currently included in the less well-understood category. That is, the guidance suggests that utilization of (currently) less well-understood adaptive methods in exploratory studies may pave the way for their future acceptance as well-understood AD. One potential practical difficulty for the implementation of this recommendation is that sponsors often design exploratory studies, especially in Phase 2, as mini A&WC studies, in the hope that if great results are observed, the study may be accepted by RA as one of the required pivotal studies. The guidance specifically discourages this type of practice.

2.2.3 Well-Understood vs. Less Well-Understood Adaptive Designs

Within the class of A&WC studies, the guidance introduces a classification of *well-understood* and *less well-understood* types of adaptive designs. This has been mistakenly interpreted by many in industry, most notably by some in regulatory affairs groups, to mean that only AD of the well-understood type would be acceptable to FDA. Even though it has been clarified by FDA representatives (involved

in the writing of the draft guidance) at public meetings and conferences that the categorization only referred to the state of regulatory knowledge of and familiarity with different types of AD at the time the draft guidance was published, the misunderstanding persists till the time of publishing of this book. There is an expectation that this issue will be addressed in the final version of guidance, when it is published.

The set of well-understood AD identified in the draft guidance is composed broadly of group sequential designs (with early termination for either demonstrated efficacy or futility) and adaptations that do not involve post-baseline unblinded data. Examples include adaption of study eligibility criteria based on baseline data, blinded sample size or study duration re-estimation, and adaptations based on outcome unrelated to efficacy (though the guidance warns that this may be difficult to ascertain). In general, adaptations based on blinded and/or baseline data (carried out by personnel without access to unblinded results) do not raise any regulatory concerns.

The fact that group sequential designs, though involving adaptations based on unblinded data, are included in the well-understood category gives further indication that the classification is more based on regulatory familiarity than acceptance. It also suggests that, as FDA is exposed to more AD trials involving unblinded adaptations, some of the methods currently in the less well-understood category may find their way into the well-understood group.

All designs involving adaptations based on unblinded post-baseline data, with the exception of group sequential designs, fall into the less well-understood category. Examples include unblinded sample size/study duration re-estimation, response-adaptive randomization, adaptive subgroup and/or endpoint selection-based observed treatment effects, and adaptive dose selection. With regard to the latter, the guidance recognizes its potential value in the context of A&WC studies (to allow some limited exploration of dose–response), provided strict control of Type I error rate can be demonstrated. Within the category of less well-understood AD, the guidance highlights designs with multiple types of adaptations and adaptations in non-inferiority studies. With regard to the first, the guidance expresses concerns related to the increasing complexity that results from combining different types of adaptations in the same study, which could lead to difficulties in interpreting the final results. The value of adaptations in the context of non-inferiority studies is acknowledged, but the guidance points out that some of the design elements in non-inferiority trials are not suitable for adaptation, most notably the non-inferiority margin.

Besides the usual concerns about potential Type I error rate inflation, bias in treatment effect estimates, and operational bias in trial conduct, the guidance also indicates the potential for Type II error rate increase in the context of less well-understood AD, citing too liberal futility rules and suboptimal dose selection as examples. Of course these are concerns that typically resonate and concern more sponsors than regulators, so it is refreshing to see them mentioned in the guidance. The discussion around less well-understood AD ends on a positive note, with the guidance stating that *cautious use of adaptive designs can advance overall development programs*. This is likely to be as supportive as one could expect to read in a guidance document.

2.2.4 Role of Trial Simulations

As well known among practitioners who have designed and/or implemented adaptive designs, modeling and trial simulations play a central role in their evaluation and the understanding of their operating characteristics. Even relatively simple AD, such as blinded sample size re-estimation, require simulations to properly characterize its performance under alternative scenarios (e.g., underlying effect and variability) and design choices (e.g., when to conduct the interim analyses). Modeling plays a central role in the characterization of alternative scenarios, such as the recruitment and dropout processes, dose–response profiles, and correlation between endpoints. The combination of modeling and trial simulation provides the backbone for the evaluation and comparison of alternative designs, including adaptive ones, and the planning of a specific adaptive design (e.g., number and timing of adaptations, impact on Type I error rate and power).

The guidance acknowledges the importance of trial simulations for the determination of operating characteristics of AD, the comparison of alternative designs to justify the selection of a particular AD, and the understanding of inferential properties of an AD. In fact, the guidance states that the reporting of trial simulations should be an important component of the documentation to be submitted to FDA when a sponsor proposes the use of an AD in the development program. The guidance goes further and indicates that the models, programs, and flow charts for possible adaptive pathways used in the simulations should also be included as part of the submitted documentation. Among the inferential characteristics of the design that can be investigated via simulation, the guidance names the impact on Type I error rate, power, and bias in the estimation of treatment effects. The document goes into some detail on the types of models that could be considered in the simulation-based evaluation of AD, including withdrawal and dropout models, models for selecting among multiple endpoints, and models characterizing the study endpoints (e.g., longitudinal models). It also includes a list of which elements should be included when reporting simulations used for AD evaluation, such as a listing of all possible adaptation branches, the design features and assumptions, and calculation of Type I error rate and power.

While discussing the importance and usefulness of trial simulations, the guidance goes on a short detour to discuss how Bayesian methods can play a relevant role in the context of AD. It indicates that Bayesian approaches provide a useful framework for describing the various choices and decisions available in an AD, placing them in a probabilistic context that is naturally handled under the Bayesian paradigm. The guidance even goes as far as to state that Bayesian decision rules can be used to guide adaptations while preserving the Type I error rate in a frequentist sense. It is unclear, though, if such framework would be accepted by regulators in the context of an A&WC study, or if it should have its use limited to exploratory studies.

On a side note that was disappointing to some, the guidance states that, though trial simulations are acknowledged as useful, or even essential, for the understanding of operating characteristics of an AD, their use to establish strict control of Type I

error rate in an AD is *controversial and not fully understood*. Because many AD are complex enough not to allow the analytical derivation of its Type I error rate, this remark in the guidance has led to lively reactions from industry. In general, the available analytical solutions rely on rather inefficient upper bounds for the Type I error rate, in the sense that the true significance level is considerably smaller than the upper bound, under a wide range of realistic scenarios. This leads to loss in power, or increases in sample size to avert it (both of which, of course, are evaluated via trial simulations).

2.2.5 Protocol and SAP for an Adaptive Design

Because of the heightened concerns about operational bias and trial integrity surrounding AD, the prospective specification of all aspects of the study design and planned analyses is of paramount importance. As frequently mentioned in the ADWG publications and also highlighted in the draft guidance, to ensure the scientific validity of an AD, any potential adaptations need to be pre-specified: *adaptive by design*, as aptly stated in Gallo et al. (2006).

The protocol of an A&WC AD study, according to the draft guidance, typically needs to be more detailed than for a conventional design. The protocol and its supportive documentation (such as the simulation report) need to contain all critical information to allow FDA to evaluate the AD. These should include

- Study rationale
- Justification of design features, including any proposed adaptations
- Operating characteristics of proposed design, such as Type I error rate and power
- Plans to ensure study integrity when unblinded interim analyses are planned
- Role of AD in overall clinical development strategy
- Objectives and design features of the AD, all possible adaptations envisioned, assumptions, analysis methods, and quantitative justification for design choices at planning stage (typically via simulations)
- Impact of adaptations on frequentist operating characteristics (e.g., Type I error rate)
- Summary of models used in planning (e.g., disease progression, dropout, dose–response)
- Analytical derivations to demonstrate strict control of Type I error rate, if appropriate (e.g., A&WC studies)
- Charter of personnel involved in carrying out adaptations and study monitoring

It is acknowledged that data monitoring committee (DMC) charters will generally need to be more detailed for an AD compared to a more conventional design involving interim analyses (e.g., group sequential design).

The extensive list of protocol elements for an AD mentioned in the draft guidance has raised some concerns about the greater scrutiny that this type of design may receive at FDA. In reality, most of the items in the guidance list apply equally

to nonadaptive designs and should be part of the checklist of good design practice. Adaptive designs have created greater awareness about the importance of proper scenario evaluation via modeling and trial simulations, which should lead to better design planning and justification across drug development, and not just for AD.

With regard to statistical analysis plans (SAP) for AD, the key message in the guidance is *prospective specification*. The guidance encourages sponsors to have the SAP finalized by the time of protocol finalization, a practice already adopted by some, but certainly not the majority of biopharmaceutical companies. Specific elements that should be included in an AD SAP listed in the guidance are the following:

- All prospectively planned adaptations
- Statistical methods to be used to implement adaptations (e.g., how to calculate a potential increase in sample size or trial duration, rule used to select a dose)
- Justification of Type I error control
- Statistical approach to be used for appropriately estimating treatment effects

The overarching message in the guidance with regard to regulating AD is that FDA understands that this type of design requires more in-depth regulatory review and evaluations. Accordingly, it is expected that sponsors will provide documentation, such as protocols and SAP, with the level of detail necessary to allow the proper regulatory oversight.

2.2.6 Interactions with FDA on Adaptive Designs

According to the guidance, it is anticipated that sponsors will need earlier and more intense interactions with FDA to discuss and reach agreement on planned AD. This will, of course, vary with the type of AD and the phase of development, being more critical for less well-understood A&WC trials. The guidance is not entirely clear on the type of meeting request that should be made for the discussion of AD. For exploratory studies, it is recommended that either a Type C or an end of Phase 2 (EOP2) meeting request be used. For an A&WC study, the guidance indicates that, when appropriate, an EOP2 meeting request should be used, but acknowledges that there will be instances in which this will not be adequate. The guidance states that a special protocol assessment (SPA) meeting would *not* be appropriate to discuss AD and discourages sponsors from submitting SPA requests for that purpose. Further clarity on the type of meeting request that would be most appropriate for engaging FDA in discussions on proposed AD would be useful to sponsors. Perhaps a new type of meeting, or the extension of existing meeting types, should be considered for AD.

The protection of study blind among trial personnel non-authorized to have access to treatment assignment during the trial is a recurrent theme in the draft guidance, identified as a critical issue to ensure the integrity and validity of an AD. The guidance indicates that SOPs specific to AD should be put in place by sponsors,

clearly indicating who will implement adaptations and how access to unblinded data during the study will be controlled (in particular, when study personnel and investigators may have access to unblinded results). The guidance highlights that an independent group from the study personnel should be responsible for unblinded interim analyses and adaptive decision making. The role can be assigned to an independent DMC (IDMC) or some other group. There is still no consensus across the biopharmaceutical industry, or among regulators on whether conventional IDMC should have their role extended to also handle AD monitoring and decision making, or if a new type of independent group should be formed for this type of study (see Chap. 14, on DMC).

2.2.7 Final Remarks

The draft guidance concludes with some specific recommendations regarding the report of the final results of an AD. There should be strict compliance with the prospectively planned adaptation process and with the procedures for ensuring study integrity, such as the preservation of treatment blinding. The final documentation submitted to FDA should include a description of the processes and procedures actually carried out in the trial, any records from deliberations of the IDMC and any other groups involved in carrying out adaptations, interim results used for adaptations, and an assessment of the adequacy of firewalls to prevent access to unblinded results by unauthorized personnel. All analyses included in the final report should strictly adhere to the SAP. Because of concerns about shifts in patient population during the study, possibly induced by adaptations, the guidance recommends that the consistency of estimated treatment effects across study stages (i.e., before and after adaptations) should be explored and reported with the final results. If potential shifts are observed, they are likely to become a review issue.

The overall message of the guidance is positive on AD while being cautious about their proper planning, implementation, and reporting. The guidance recommends that sponsors keep AD simple, avoiding too many or too complex adaptations in the same trial. It encourages increased planning and early interactions with FDA, especially for more complex A&WC studies. Assurance that treatment blinding is preserved and adequately documented is paramount to regulatory acceptance of the results from an AD.

2.3 EMEA Reflection Paper on Adaptive Designs

The EMEA reflection paper played a pioneering role with regard to regulatory guidance on adaptive designs, being published at a time of active discussion on different aspects of adaptive designs, such as methodology, implementation, and regulatory acceptance. The EMEA document shed some critical light into the discussions

taken place then and, in many ways, paved the way for the FDA draft guidance published years later. The EMEA document is considerably narrower in scope and less detailed than the FDA draft guidance. On the other hand, it emphasizes some regulatory concerns about AD that are only tangentially discussed in the FDA document, making it a useful complement to the latter with regard to regulatory thinking on AD at the time this book was published. This section summarizes the key points in the reflection paper, contrasting them to the FDA draft guidance and considering them from an industry perspective.

The EMEA document focuses almost exclusively on confirmatory trials, or, in the notation of the FDA draft guidance, A&WC studies. The overall tone of the document is accepting of the potential utility of AD, but with clear concerns about their adequate implementation in clinical trial practice. By comparison, the reflection paper is less encouraging about AD than the FDA guidance, but it does not strike a negative tone with regard to their utilization, when properly planned, conducted, and analyzed. In its opening remarks, the EMEA reflection paper recognizes that AD have the potential to speed up drug development and more efficiently allocate resources, without compromising the scientific and regulatory standards, while highlighting that the basis for regulatory decision making will need to be improved to allow AD to be fully embraced by regulators. A less encouraging comment in the opening section of the document is that AD in the context of confirmatory trials is a contradiction in terms, as one should not need to adapt what is to be just confirmed. Of course this is too narrow a view of the regulatory dichotomization between the exploratory and confirmatory phases of development, being toned down in later sections of the document. It is not the case in drug development practice that all is known about a compound before it is taken into Phase 3 studies—development programs would take substantially longer, and approved drugs would cost significantly more, if this narrow interpretation of the regulatory process were to be followed to the letter.

An important and interesting difference between the EMEA reflection paper and the FDA draft guidance is the focus of the former on the assessment of homogeneity between stages of an AD. The issue is certainly discussed in the FDA draft guidance, but with considerably less prominence than in the EMEA document, where it appears to be central to the regulatory acceptance of AD. There are, of course, more similarities than differences between the EMEA and FDA documents and certainly no disagreement between them with regard to recommendations and regulatory requirements.

The EMEA reflection paper is less didactic than the FDA draft guidance, with no attempts at classifying AD, like is done in the latter. A more formal definition of adaptive designs is only included in the last page of document and it illustrates the narrow view of the document: "a study design is called '*adaptive*' if statistical methodology allows the modification of a design element … at an interim analysis with full control the type I error." It is clear from this definition that the main concern in the document about the validity of an AD is the preservation of strict control of Type I error rate in the presence of possible adaptations. The definition of AD presented in the FDA draft guidance is much broader in scope and more in line with mainstream publications in the field.

The concern about potential operational bias induced by an AD is shared between the EMEA and FDA documents, though in the former such concern is almost

exclusively associated with the possible change in patient population during the study. The document states that if substantial differences are observed in patient composition (e.g., demographics, baseline characteristics) and/or in trial results before and after an adaptation then there would be serious regulatory concerns about the validity of the final conclusions and the integrity of the study as a whole. It is not clear, though, what would characterize a *substantial difference* in this context, or whether it should be formally tested via a hypothesis test, or just explored via summary statistics and estimated effects. There is a clear tone of discouragement of unblinded interim analyses in the reflection paper, because of the perceived risks of information leak resulting from them. The recommendation is that unblinded interim analyses only should be used when there is a clear, justifiable need, should be kept to a minimum number, and with the flow of unblinded information should be carefully documented and controlled. One is left to wonder if the regulators who produced the reflection paper would find the implementation of an AD as sufficient reason to justify the inclusion of interim analyses in the study.

It is possible (and, one would hope, likely) that regulatory thinking at EMA has evolved since the publication of the reflection paper and a more accepting view of the ability of sponsors to preserve the blind in an AD and avoid the leaking of unblinded results via appropriate processes and firewalls now prevails. If that is the case, one would expect a more positive view of unblinded interim analyses, not only in the context of AD, but in confirmatory trials, more broadly. Interestingly, the reflection paper seems to be supportive, or at least not discouraging, of group sequential designs, which, of course, require unblinded interim analyses.

A topic discussed in the EMA reflection paper but omitted from the FDA draft guidance is that of overrunning, i.e., observed data on certain patients only becoming available after a decision to stop the study at an interim analysis point was made. This may be because overrunning is a topic that has been extensively discussed and addressed in the context of group sequential designs, being less of an issue in AD that do not include an early efficacy stopping rule. Of course, it is a nonissue in the case of futility stopping.

Similarly to the FDA draft guidance, the EMEA reflection paper states that any adaptation under consideration should be pre-planned, be properly justified in the context of the development program, and have their number kept to the necessary minimum. Strict control of Type I error rate is indicated as a prerequisite for the regulatory acceptance of any AD, but appropriate statistical methods for treatment effect estimation (point-wise and confidence intervals) in the context of an AD are also necessary. The reflection paper stresses at various points that AD should not be used as a substitute for good planning and thorough exploration in early phases of clinical development.

The reflection paper names and discusses a number of specific types of adaptations, a subset of which are briefly summarized below.

- *Sample size re-estimation*: The blinded version should be used whenever possible, but the unblinded alternative can also be considered, when properly justified. In either case, there should be good justification of why the use of this type of adaptation is not an indication of just insufficient investigation in exploratory studies.

- *Change or modification of primary endpoint*: This would be very difficult to justify in practice and would likely lead to difficulties in statistical inference if one were to combine results from stages utilizing different endpoints (e.g., rejection of a global null hypothesis).
- *Discontinuing treatment arms*: Discontinuing the placebo arm after an interim analysis is discouraged, as it may result in changes in patient population and lead to inferential hurdles at the end of the study; unbalanced randomization favoring active treatment over placebo throughout the study should be considered as an alternative. Multiple comparison approaches are required to properly control the Type I error rate.
- *Phase 2/3 combinations*: The reflection paper suggests that Phase 2/3AD are in principle acceptable, but need to be properly justified (and with any AD mentioned in the document) and would not provide sufficient evidence of efficacy for regulatory approval if it were the single pivotal study conducted in the program. That would be the case even in indications in which a single Phase 3 study could be accepted for approval. The use of two Phase 2/3AD studies is mentioned as a possible path for approval, though it may be challenging to ensure that the same decisions are reached in both trials. One assumes that the combination of one Phase 2/3AD design with one conventional Phase 3 design would also provide sufficient evidence of efficacy for regulatory approval. Single Phase 2/3AD studies could be considered for orphan indications.

The FDA draft guidance does not contradict any of the recommendations included in the EMEA reflection paper, but it certainly strikes a more positive note on the regulatory acceptability of and support for adaptive designs. One of the possible reasons explaining this difference in tone between the two regulatory documents is that the FDA document was crafted following innumerous discussions with industry groups focused on AD at scientific meetings and through visitations to FDA, as well as several white papers published by those same industry groups. The EMEA reflection paper did not benefit from the same level of open dialog between industry representatives and regulators on methodological and operational issues related to AD, and may reflect a more one-sided view on AD.

2.4 Industry Reaction and Perspectives on Guidance Documents

The biopharmaceutical industry, by and large, regards adaptive designs as a useful tool for its ongoing effort to modernize and improve the efficiency of drug development. Clear regulatory guidance on the acceptability, or not, of different types of AD is a precondition for the effectiveness and viability of these methods in practice. Therefore, both the EMEA reflection paper and the FDA draft guidance on AD were well received by industry, despite the less than encouraging tone of the former and the ambiguity of some elements in the latter. They were perceived as an encouraging

sign of regulatory agency acknowledgement of the potential benefits of AD while providing some level of guidance on how to possibly address regulatory concerns about their use in clinical development practice.

Following the release of the regulatory documents, industry groups were organized and collated their concerns and suggestions on the guidance documents, submitting them during the corresponding comment periods. Some of those suggestions have been implemented in the published version of the EMEA reflection paper. The final version of the FDA draft guidance had yet to be released at the time of publishing of this book, being unclear on which, if any, of the industry suggestions would be incorporated in the revised document. We review here the comments and suggestions collated for each of the documents by PhRMA industry groups, following the same order used previously in the paper, namely starting with the FDA draft guidance, followed by the EMEA reflection paper.

2.4.1 FDA Draft Guidance

By the time the draft guidance was released, the ADWG was no longer affiliated with PhRMA, so a new group needed to be formed to review and produce the PhRMA response to the document. However, the majority of the PhRMA review team was composed of former members of the ADWG, so a certain level of continuity was achieved in the response to the FDA draft guidance submitted by PhRMA.

The overall reaction of the PhRMA review team (and industry as a whole) to the draft guidance was positive, with the group acknowledging that the document was quite helpful in clarifying FDA's position on and concerns about AD, and with the expectation that the guidance would positively impact the broader acceptance and proper utilization of AD in clinical drug development. There were also a number of comments, concerns, and suggestions for improvement put forward by the PhRMA review team, summarized below.

The main concern was the categorization of adaptive designs for A&WC studies into well understood and less well understood. The team indicated the fear that less well understood would be misunderstood as not-to-be-used by many in industry, which unfortunately turned out to be the case. A suggestion was made for FDA to clarify in the final version of the guidance that, when properly planned, implemented and analyzed, less well-understood AD were also acceptable for A&WC studies. Furthermore, one would expect that as FDA became more familiar with the appropriate utilization of those AD, they would be moved to the well-understood category in possible future revisions of the guidance. One point raised by the review team was that many of the cautions indicated in the guidance for less well-understood AD (e.g., potential for operational bias after unblinded interim analyses) also apply to well-understood AD (e.g., group sequential designs) and even conventional, non-adaptive designs. Adaptive designs may have motivated greater awareness and discussion around such issues, but they are not exclusive, or even more prevalent in AD.

While the draft guidance is clearly encouraging of the use of AD in exploratory studies, the message is somewhat ambiguous with regard to A&WC studies.

The many references to bias in the context of AD for A&WC studies (operational, estimation, and in hypothesis testing) go beyond cautionary to strike a somewhat negative tone. The PhRMA review team suggested that the final guidance included a clear message of FDA's willingness to consider AD both for exploratory and A&WC studies.

The lack of clarity in the guidance about which type of meeting request would be appropriate for discussion and review of AD with FDA was another important point raised by the PhRMA review team. The group suggested that there should be greater clarity in the final version of the guidance on how sponsors should seek input from FDA on AD with different degrees of complexity and the circumstances under which an SPA would be the appropriate type of meeting for such interactions.

The Biotechnology Industry Organization (BIO) also formed a review team that produced an industry response to the FDA draft guidance. The comments and suggestions submitted by the BIO review team were broadly similar to those of the PhRMA group, with a few noteworthy additions. The BIO group made the recommendation that, to avoid potential confusion, methods and statistical and logistical consideration for AD be separately described in the guidance for exploratory and A&WC studies. In addition, the review team suggested that there should be better balance between exploratory and A&WC AD studies in the document—the draft guidance focuses mostly on the latter (which is understandable, from a regulatory perspective).

2.4.2 EMEA Reflection Paper

The PhRMA response to the reflection paper was mostly driven by the ADWG, which was still affiliated with the trade association at the time the document was released. The comments from the PhRMA team were more directly targeted at defending certain types of AD and related implementation practices, compared to what was included in the PhRMA response to the FDA draft guidance. This reflects the less positive tone of the reflection paper on adaptive designs and practices.

Adaptive seamless Phase 2/3 designs were prominently discussed in the PhRMA response, reflecting the industry mindset at that time. The naming of this type of design has changed since, to avoid the explicit reference to combining exploratory and confirmatory phases in one study (though the essence of the AD remains very much present in clinical development). Regulators expressed concern about having exploratory elements (i.e., Phase 2) in a study intended to be confirmatory. An example of new naming for this type of design is adaptive A&WC study with dose/subgroup selection. In their response, the PhRMA review team lists the benefits of this type of AD, including increased information on doses and efficacy prior to triggering the confirmatory stage, reduced development timelines and costs (compared to running separate Phase 2 and Phase 3 studies), more safety information, and increased chance of treating patients in the trial with efficacious and safe drugs (see Chap. 20 for an example of a successful seamless two-stage design). The response

also included a discussion of possible regulatory strategies for including an adaptive seamless Phase 2/3 trial as one of the pivotal studies in a submission. Some of the suggestions were incorporated in the final version of the reflection paper published by CHMP.

The PhRMA review team defended the opportunity for limited sponsor involvement in interim decision making during an AD, pointing out that IDMC members may not be prepared, or willing, to make decisions that have important commercial implications to sponsors. Processes and safeguards that would allow this type of limited sponsor involvement to take place while protecting the integrity of the study are proposed in the team's response (and have been presented and discussed in white papers published by the ADWG, such as Gallo et al. 2010; see also Chap. 14 for more recent thinking on DMC for AD).

The potential for operational bias as a result of a poorly planned and/or implemented AD was acknowledged by the PhRMA review team, but they pointed out that this risk is also present with classic group sequential designs and has long been successfully addressed by sponsors. The team suggested that the potential for operational bias in an AD should be prospectively mitigated via design and implementation safeguards discussed and agreed upon with regulators prior to the start of the study, and not via post-trial assessment of changes in patient population during the study (which may occur irrespective of and unrelated to adaptations).

The response from the PhRMA review team included a suggestion to have AD for confirmatory studies classified into two categories of regulatory support: acceptable and possible. Blinded sample size re-estimation and subgroup selection were cited as examples of regulatory acceptable AD, while unblinded sample size re-estimation was mentioned in the possible category. The intention of the suggestion, at the time, was to request clear regulatory guidance on what types of AD were endorsed by EMA and which would require further justification and discussions with regulators. Even though this suggestion was not implemented in the final version of the reflection paper, it possibly provided the seed for the classification of AD A&WC studies into well understood and less well understood. In hindsight, the suggestion may not have the most beneficial for advancing the broader use of AD, from an industry perspective.

Additional comments and recommendations on the reflection paper put forward by the PhRMA review team were related to adaptive dose-finding designs (use of parsimonious modeling), unblinded sample size re-estimation (should not be ruled out as a valid AD), and Bayesian approaches (to be included in the reflection paper and have its potential use in AD discussed).

2.5 Concluding Remarks

The regulatory guidance documents on AD published to date have had a critical impact on the acceptance and utilization of AD by the biopharmaceutical industry. Both documents, in particular the FDA draft guidance, have helped clarify the

regulatory position and concerns on AD, which by itself is quite useful. However, the cautionary tone of both documents and the classification of some AD for A&WC studies as less well understood in the FDA guidance have caused some negative reaction in industry with regard to regulatory acceptance of AD, more generally. As a result, the increased utilization of AD that was expected after the release of the FDA draft guidance never materialized.

One important change that has occurred from the time prior to the release of the FDA draft guidance is that the ADWG is no longer affiliated to PhRMA and, perhaps for this reason, no longer active with regard to scientific advocacy for adaptive designs. The publication of the final version of the FDA guidance which addressed the key industry concerns listed in Sect. 2.4.1 would go a long way toward increasing the acceptance and utilization of AD in industry. We hope that FDA will be able to provide industry advocates of AD with this valuable support soon.

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