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PANEL 1

Data Submission Standards and Evidence Requirements

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Importance of streamlining data collection

The goal of FDA guidance documents is to provide insight into the data necessary for FDA reviewers to reliably assess the risk-benefit ratio of an investigational agent for a particular clinical indication. The current U.S. Food and Drug Administration (FDA) registration guidance for cancer therapy trials does not completely describe the level of detail necessary for informative data capture to support claims of safety and efficacy for supplemental indications of new cancer treatments[1]. The guidance, as currently set out, does not distinguish between drugs with substantive safety information and definite benefit to patients from drugs with limited safety data which may carry safety risks that have not yet been recognized. Data collection requirements, thus, become essentially the same whether for a primary indication or a supplemental application. This can result in collection of excessive and sometimes unnecessary data by investigators, particularly for trials designed to explore additional indications where substantial toxicity data about an agent already exist. Further, since there is no established standard for collection of data in support of supplemental applications, sponsors interpret the requirements variably resulting in inconsistent quality and quantity of data. Frequently the data collected do not result in modifications to FDA labeling or inform medical practice yet the data collection requirements add complexity and cost to conducting the study. Therefore, optimized standards for data collection should be developed for well-studied cancer therapies to improve the efficiency of safety evaluations without sacrificing the scientific integrity and validity of study results.

Streamlining data collection will help ensure better patient safety by improving the overall quality of data submitted in supplemental applications. Collecting essential data that will help inform patient safety such as toxicities leading to death or dose discontinuations is more important than collecting large amounts of data such as cataloguing all mild adverse events that ultimately adds little information to the existing safety profile of the drug. Collection of unused data may actually distract from gleaning crucial information. When faced with large amounts of safety data, it becomes difficult to prioritize safety events; distracting sites from focusing on the collection of important information such as understanding what makes physicians or patients modify or stop treatment. Thus, large amounts of data can sometimes obfuscate knowledge of new and relevant safety data. Furthermore, streamlining data collection will greatly reduce the administrative burden on the clinical trial system and will focus finite resources on collecting key data elements. Reducing burdensome and unnecessary data collection will improve physician participation in clinical trials. Surveys to understand why patients do not participate

in clinical trials reveal that doctors often do not recommend clinical trials to their patients. Among various other reasons, doctors cite that they are weary of the high administrative workload and liability associated with conducting clinical trials. In an effort to understand the burden of excessive data collection on trial administrators, a working group; resulting as an outgrowth of the 2008 Conference on Clinical Cancer Research and formed under the aegis of ASCO; solicited input from several cooperative group and industry sites. Of 110 responses received to the poll, over 85% expressed the view that data optimization (as recommended below) would moderately or significantly impact site resources, allowing collection of higher quality targeted data and greater participation in the clinical trials process[2].

Potential Tradeoffs of Data Optimization

In order to further explore the tradeoffs between complete and optimal data collection, the data optimization working group assessed the extent of safety data collection necessary and sufficient to inform clinical and regulatory decisions in a supplemental application with the basic assumptions that:

- Streamlined toxicity data collection will not be used for initial indications (or the first supplemental application following accelerated approval)
- Streamlined toxicity data collection will only be used if the prior approval process included a safety database that was acceptable for a full regulatory approval
- The statistical analysis plan will be structured to minimize the risk of missing important safety signals
- Serious Adverse Events (SAEs), deaths, dose modifications and/or discontinuations (with reasons) will be collected for all patients on all study arms.
- Targeted Adverse Events (AEs) would be collected based on the known safety profile and pharmacology of the drug and the study patient population.

Streamlining data collection will ensure that the data collected will be utilized and that unnecessary data will not be collected. Data collection requirements will vary as necessary depending on whether a sufficiently large safety and drug interaction profile already exists, the similarity of the study population to the population for approved use, the similarity of the supplemental regimen to the regimen already approved and, finally, whether the supplemental application follows initial full or accelerated approval. By collecting SAEs, deaths, dose modifications and/or discontinuations and targeted AEs of interest in all patients on all study arms, sponsors are reasonably as likely to detect important safety signals as with the current data collection process.

Study Organization and Participants

At the Conference on Clinical Cancer Research held in September 2008, a panel on "Data Submission Standards and Evidence Requirements" proposed a framework for data collection necessary to support claims of safety and efficacy for supplemental New Drug Applications and Biologic License Applications (sNDAs/sBLAs)[3]. In order to further explore elements of that framework, the American Society for Clinical Oncology (ASCO) formed the Data Optimization Working Group. The working group provided a forum for all interested stakeholders (FDA, NCI, academia, industry, and advocacy) to retrospectively review data sets from completed phase III trials, many that were used for FDA supplemental approvals, and discuss potential revisions to data collection standards.

Four companies and one cooperative group collaborated on this project. A statistical analysis plan was developed, reviewed by FDA, and used by all participating sponsors. The project involved a re-analysis of eight trials, in both metastatic and adjuvant settings, studying cytotoxic chemotherapy, targeted biological therapy and hormonal therapy as shown in the tables below[4].

Table 1: Candidate Trials evaluated in the study in the Metastatic setting

Candidate Trials - Metastatic					
Company	**Candidate Study**	**Patient Population**	**Treatment**	**Trial Size**	**Primary End point**
Genentech	AVF2107g	1st Line mCRC	Arm 1: irinotecan/5-FU/LV (bolus-IFL) + placebo Arm 2: bolus-IFL + rhuMAb VEGF Arm 3: 5-FU/LV + rhuMAb VEGF	813	OS
Genentech	ECOG 4599	1st Line non-squamous NSCLC	Arm 1: Paclitaxel/Carboplatin Arm 2: Paclitaxel/Carboplatin + Avastin	878	OS
Genentech	AVAIL	1st Line non-squamous NSCLC	Arm 1: Cisplatin/Gemcitabine Arm 2: Cisplatin/Gemcitabine + Bevacizumab	656	PFS
GSK	EGF 30001	mBreast	Arm 1: Paclitaxel + Placebo Arm 2: Paclitaxel + Lapatinib	580	TTP
Lilly	JMDB	1st Line NSCLC	Arm 1: Cisplatin plus Pemetrexed Arm 2: Cisplatin plus Gemcitabine	1669	OS

* OS: Overall Survival, PFS: Progression Free Survival, TTP: Time to Tumor Progression

Table 2: Candidate Trials evaluated in the study in the Adjuvant setting

Candidate Trials - Adjuvant					
Company	**Candidate Study**	**Patient Population**	**Treatment**	**Trial Size**	**Primary Endpoint**
Novartis	BIG 1-98	PMP women with HR+ EBC	Arm 1: Femara (letrozole) Arm 2: Tamofen (tamoxifen)	8028	DFS
CALGB	89803	Patients with resected adenocarcinoma of the colon	Arm 1: LV + 5-FU 500 Arm 2: Irinotecan + LV 20 mg/m2 + 5-FU	1264	OS
Genentech	HERA	HER2+ adj breast cancer	Arm 1: Observation Arm 2: Herceptin	3386	DFS

* OS: Overall Survival, DFS: Disease Free Survival

Study Findings & Recommendations

The purpose of this study was to determine whether important safety information would be lost by only gathering toxicity data on a subsample of patients enrolled in a supplemental NDA trial with a drug for which a substantial toxicity profile already exists. In candidate trials where sub sampling is appropriate, it is assumed that SAE information including all deaths, dose discontinuations and modifications along with the associated reasons would continue to be collected on all patients. The re-analysis demonstrated that data sub-sampling did not appear to omit important information about the safety profile, i.e., similar conclusions regarding the safety profile would have been reached if a sub-sampling approach had been used.

The study identified statistical methods for determining appropriate sub sampling sizes that can be scaled to fit different cut-off rates. The table below shows subsampling size range recommendations using this statistical methodology.

Determining Sub Sampling Size (Assuming 2% excess; 2-arm trial)

- In the metastatic setting, approximately 400 – 500 patients should be sub sampled (full study size of 800-1200 patients)
- In the adjuvant setting, a total size of approximately 400-900 patients should be sub sampled (full study size of 800-6000 patients)
- Sub sampling may not be appropriate / or advantageous for trials with fewer than 600 patients.

The study also examined various subsampling methods such as sampling patients at random, study centers at random, patients at the largest centers, first patients enrolled, last patients enrolled and the first and last patients enrolled (last patients enrolled and the first and last patients enrolled were only analyzed for comparative purposes – not as a practical methodology). Sampling by centers at random was determined to be the most logistically feasible and accurate methodology for sub sampling. To ensure full representation, a stratified population of patients from small, medium and large centers should be chosen.

A lack of consensus regarding data collection, specifically toxicity data, has led to a frequent discordance between practices in NCI cooperative groups and industry-sponsored clinical trials. The goal of this project is to recommend and justify sufficient data collection to generate safety data for drug labeling and clinical use and to reduce collection of unnecessary data elements in supplemental NDAs and BLAs. The effort and resources saved can be better channeled to focus on collecting more meaningful and accurate information that informs clinical and regulatory decisions and leads to greater participation in the clinical trials process.

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FDA Response

In a guidance published in 2001 (Cancer Drug and Biologic Products—Clinical Data in Marketing Applications), FDA provided recommendations for sponsors on data collection for cancer clinical trials submitted to the Agency to support marketing claims in new drug applications (NDAs), biologics license applications (BLAs), and supplemental applications for new drug and biologics indications. The regulations (21 CFR 314.50) require that supporting data be submitted with study reports from well-controlled trials, but they do not describe the amount and type of data that should be collected.

Commercial sponsors may collect large amounts of information to ensure that they have all the data that regulatory agencies might request. Non-commercial organizations, for example, United States cooperative groups frequently collect less information than commercial entities, although their trials may provide adequate data for important risk/benefit assessments supporting regulatory approvals. FDA recognizes that extensive data collection can be expensive and time-consuming and that collection of unnecessary data is not an optimal use of clinical trial resources.

In the 2001 guidance, FDA acknowledged that it is not possible to provide precise data collection requirements that could be applied to all trials because of the complexity and variability of clinical trial design. FDA strongly encouraged sponsors to develop specific proposals for data collection and discuss their proposals with the Agency prior to initiating clinical trials. FDA maintained that agreement between the Agency and the sponsor of drug or biologic on pre-specified data collection plans would “avoid the collection of unnecessary information, allowing resources to be directed toward studying important endpoints.”

As discussed in the 2001 guidance, the following factors should be considered when assessing what data elements are necessary to collect:

- The type of regulatory submission (e.g., new marketing application versus efficacy supplement).
- The similarity of the proposed new use of the drug to already approved uses of drugs.
- The population being studied (e.g., patients in the surgical adjuvant setting, patients receiving first-line treatments, or patients with refractory disease).
- The amount of available supplemental information from other sources on the safety of the drug, such as data from trials in a similar population.

The goal of the project on Data Submission Standards and Evidence Requirements (Panel 1) was to identify the scope of data collection sufficient to generate safety data for drug labeling and clinical use and to reduce collection of unnecessary data elements in supplemental NDAs and BLAs. A study was conducted to determine whether important safety information would be omitted by collecting data on a subsample of patients enrolled in trials to support supplemental BLAs or NDAs for approved drugs with extensive safety information already available. Data sampling did not appear to omit safety information that would be needed for labeling or the benefit/risk evaluation.

Although this study focused on supplemental NDAs and BLAs for cancer drugs, FDA believes that these findings could apply to safety data collection for supplemental NDAs and BLAs for all therapeutic drug classes. Safety data collection from all subjects would still be needed for initial marketing claims for NDAs and BLAs. However, based on the factors outlined in the guidance (i.e., type of submission, similarity of proposed use to approved use, population being studied, available additional information for other sources), it should be possible to more narrowly focus the scope of data collected without a detrimental impact on the regulatory evaluation of supplemental marketing applications of drugs or biologics.

FDA is committed to developing guidance applicable to all therapeutic classes. That guidance will further clarify and illustrate the principles outlined in the 2001 guidance for cancer drugs and biologics, as well as incorporate the findings from the Data Submission Standards and Evidence Requirements project.

References

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[2] Schilsky.R, Presentation at American Society of Clinical Oncology, July 30, 2009
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[4] A detailed manuscript for submission is currently in preparation under the leadership of the Working Group.