March 11, 2014

Position Statement: PhRMA Principles to Govern Pharmaceutical Company Support of Investigator Initiated Studies

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is pleased to present this paper setting forth suggested principles for the regulation of industry support of Investigator Initiated Studies (IIS's). PhRMA is a voluntary, non-profit association that represents the leading pharmaceutical research and biotechnology companies in the United States, which are devoted to inventing medicines that allow patients to live longer, healthier and more productive lives. Member companies are leading the way in the search for new cures. In 2012 alone, PhRMA members invested over $48.5 billion in discovering and developing new medicines.

I. Introduction

PhRMA and its member companies are firmly committed to conducting high quality, scientific, and ethical clinical research in a manner that respects and protects the rights, dignity, safety and welfare of all study participants in full compliance with applicable laws and regulations, as well as commonly accepted global standards, wherever in the world clinical trials are performed. PhRMA and its member companies believe that a meaningful research objective, a scientifically valid design, adherence to fundamental ethical principles, respect for local norms and culture, compliance with applicable legal and regulatory requirements, and high quality execution should result in the conduct of research that is valid, reliable and ethically acceptable in any country.

In 2002, PhRMA adopted the *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* ("PhRMA Principles"). These Principles, which are based on standards established by the Declaration of Helsinki and the International Conference on Harmonization's ("ICH") Guideline for Good Clinical Practice, reinforce the pharmaceutical industry's "commitment to the safety of research participants" and "to sponsoring clinical research that fully complies with all legal and regulatory requirements." [1] The PhRMA Principles have been revised twice since their adoption in 2002.

Research is critical to the discovery and development of new therapies. Although the pharmaceutical industry conducts or sponsors a substantial proportion of clinical research worldwide, many important studies are sponsored or conducted by independent researchers and institutions, sometimes with support from pharmaceutical companies. PhRMA believes it is important for this research, like company-sponsored research, to be conducted responsibly in accordance with internationally recognized standards, such as the Declaration of Helsinki and the ICH's Guideline for Good Clinical Practice.

[1] Pharmaceutical Research and Manufacturers of America, *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results*, at 2-3 (2009) (hereinafter "PhRMA Principles")

PhRMA fully encourages industry support of pharmaceutical research and recognizes the importance of fostering productive relationships in research while also ensuring that any investigator or IIS is not biased by such support. PhRMA, however, encourages to distinguish when a pharmaceutical company is sponsoring a study versus providing appropriate support for an IIS.

Moreover, because IIS's entail unique issues and challenges, PhRMA fully supports to ensure the objectivity and credibility of pharmaceutical research conducted in Japan. We believe that the goal of IIS regulations should be to help maintain the objectivity of research while also allowing investigators to consult with and utilize the collective knowledge, experience, and resources of pharmaceutical companies. In this paper, we present PhRMA's views and specific recommendations, informed by the principles of the ICH, on the regulation of industry-supported IIS's.

II. Suggested Principles to Govern Pharmaceutical Company Support of Investigator Initiated Studies

A. Scope

PhRMA believes that Japanese industry and/or regulators should issue clear regulations governing "Investigator Initiated Studies," or "IIS's," which are defined as studies where the sponsor is an investigator, not a pharmaceutical company. According to the ICH's Good Clinical Practice (E6) guidelines, a sponsor is the party who takes responsibility for the initiation, management and/or financing of the study. PhRMA believes that the term IIS should be defined to encompass a variety of studies, including non-clinical studies (*in vitro* or animal studies), clinical studies, and observational studies. Accordingly, PhRMA supports the application of IIS regulations to any such studies where an investigator is the sponsor. In contrast, IIS regulations should not apply to studies where a pharmaceutical company acts as the sponsor of the study, whether or not for regulatory submission, including contracted research and collaboration agreements, nor should they apply to support for independently selected studies (*kenkyu josei*) or educational grants (*shogaku kifu*), since these are already governed by existing regulatory requirements. For the avoidance of doubt, IIS in this statement does not include any investigator initiated study for the purpose of regulatory submission.

B. Relationship between the investigator and a supporting pharmaceutical company

To ensure the objectivity and credibility of research in an IIS, it is critical that the investigator be independent. For example, the investigator should not be an employee or officer or be otherwise affiliated with any pharmaceutical company that has an interest in the outcome of the study. Likewise, the investigator should not have an undisclosed conflict of interest in the outcome of the study.

When deciding whether or not to support a proposed IIS, pharmaceutical companies should not preferentially select investigators who are customers of the supporting pharmaceutical company's products. Moreover, the approval of a proposal or protocol for an IIS should not be conditioned upon the purchase of the pharmaceutical company's products. To the extent

possible, the conduct of an IIS should be separated from any commercial interests or relationships between an investigator and a supporting pharmaceutical company.

C. Initiation and management of the IIS

As a general practice, pharmaceutical companies should not solicit research projects, study descriptions, or protocols from investigators or institutions and should not plan for specific new IIS's during the company's clinical or marketing planning process. However, the pharmaceutical company may publicly disclose the general areas or types of studies that it does or does not support and may answer questions from investigators about the availability of support for research.

The investigator should design the study and prepare the protocol. In contrast, the supporting pharmaceutical company should not be responsible for the initiation of the study and generally should not participate in the scientific design of the IIS, in the creation of the protocol or management of the study. However, where the pharmaceutical company's products or compounds are used in the IIS, the company should be allowed to review protocols and provide scientific comments as well as answer questions and provide information related to the safety or safe use of the products or compounds.

For any industry-supported IIS, the pharmaceutical company and the institution where the IIS will be conducted should enter into a written agreement, setting forth the terms and conditions, confirming that the research will be performed in compliance with all applicable regulatory requirements. The agreement should also include the protocol as agreed to by the company and the ethical review board. The IIS protocol, agreement, deliverables, and any references to the data or the study should disclose the fact that the IIS is financed by the pharmaceutical company.

If any regulatory approval or license is required, or if any internal approval or license of the institution of the investigator is required, such approval or license for the IIS should be secured by the investigator rather than the pharmaceutical company. The investigator or the investigator's institution should obtain informed consent from patients and should be liable for any health injuries and adverse events caused during the study. The investigator should provide periodic updates to the pharmaceutical company. Moreover, the investigator should provide written confirmation of approval of the ethical review board, and, if applicable, institutional animal care and use committee. Confirmation should include the following:

- A copy of the ethical review board approval or favorable opinion
- A copy of the ethical review board reapprovals or reevaluations with favorable opinion
- A copy of the ethical review board withdrawal of approval or favorable opinion or suspension of the study.

D. Restrictions on support by pharmaceutical companies

Any financial support should only be made for legitimate, reasonable, and necessary study activities incurred as part of the IIS, and in amounts that are no more than the fair market value for the study activities of the IIS. All funding from the pharmaceutical company should be used only for the purpose of the particular IIS, and not for any other purposes. In principle, financial support for an IIS should be paid in stages based on pre-determined milestones or deliverables to reflect the work actually performed, and not in a lump sum at the beginning of the study. Payments should be made to the institution, not to the individual investigator or any third party, and any unused funds should be returned to the pharmaceutical company.

The pharmaceutical company should not provide labor that could be considered to have material monetary value, including such services as data/statistical analysis. It also should not provide equipment or other capital resources that could continue to be used by the institution for other purposes after completion of the IIS, except for items of equipment that will be depleted during the course of the IIS. For studies in which a pharmaceutical company's products or compounds are used, any unused or excess products or compounds should be returned or destroyed as directed by the pharmaceutical company.

E. Review and ownership of deliverables

Ownership of deliverables should also be specified in the IIS agreement. In principle, the deliverables of the IIS will belong to the investigator's institution. However, the pharmaceutical company may be granted certain rights to use the deliverables either in consideration for the IIS funding or for an additional fee. In some cases, e.g., where the pharmaceutical company's compound/product is used, the deliverable may belong to the pharmaceutical company.

In all cases, the pharmaceutical company should be given an opportunity to review and comment on draft versions of the interim and/or final deliverables, which may include abstracts, final reports, or manuscripts, before presentation or publication.

III. Conclusion

PhRMA believes that the recommendations outlined above would help to ensure that industry support of IIS's is appropriate and transparent, and fully aligned with international norms as reflected in the ICH's Guideline for Good Clinical Practice. Accordingly, this PhRMA position statement would further our shared interests of maintaining the credibility and integrity of pharmaceutical research in Japan.