In 2013, the US Food and Drug Administration (FDA) proposed a structured framework to evaluate evidence of the benefits and risks of drug and biologic products (hereafter referred to as "the framework"). The framework provides a standard format for the collation and presentation of the summary information (both data and assessor opinion) included in the application. The intent of the framework is to provide consistency among assessments and transparency in the information the Agency has considered in reaching a decision.

The framework specifies a description of the disease condition, including its severity and impact on quality of life; current treatment options, including how well patient medical need is being met currently at the population level; product benefits, including the clinical relevance of the endpoints and how they relate to how a patient feels, functions, survives, and how clinically meaningful the benefit is overall and by subpopulation; risks, including characterization of the main safety concerns; a discussion of the strengths, limitations and major uncertainties in the evidence regarding benefits and risks; and a description of proposed risk management activities.

As part of a Prescription Drug User Fee Act (PDUFA) V commitment, the FDA hosted a public workshop on September 18, 2017 to review the status of its implementation of the framework. The meeting focused on experiences of FDA, industry, and other regulators in: 1) implementing the framework and other benefit-risk assessment tools, and (2) incorporating patient perspectives into benefit-risk assessments. Three additional topics were discussed during the final session of the meeting: (1) the potential application of decision-scientific methods to inform benefit-risk assessments, (2) quantitative methods for conducting benefit-risk assessments, and (3) the methods for communicating benefits, risks, and benefit-risk assessments to patients and the general public.

The International Society for Pharmacoepidemiology (ISPE) is an international, nonprofit, professional membership organization dedicated to promoting the health of the public by advancing pharmacoepidemiology, the science that applies epidemiological approaches to studying the use, effectiveness, and safety of drugs in human populations. ISPE is firmly committed to providing an unbiased scientific forum in which to consider the views of all parties with interests in drug, biologics, and devices development, delivery, use, costs and value, adverse and beneficial effects, and therapeutic risk management. Moreover, the Society provides an international forum for the open exchange of scientific information among academia, government, the pharmaceutical industry, patients and other interested members of the public for the development of policy, education, and advocacy in the field of pharmacoepidemiology and related disciplines, including such areas as pharmacovigilance, risk communication, drug utilization research, comparative effectiveness research, and therapeutic risk management. The Society's more than 1,500 members represent 45 countries. ISPE members work in academic institutions, the pharmaceutical industry, service providers, government agencies, and non-profit and for-profit private organizations and institutions. ISPE members are researchers with background and training in epidemiology, biostatistics, medicine, public health, nursing, clinical pharmacology, pharmacy, law, and health economics.

These comments were developed by members of ISPE who are part of the Benefit Risk Assessment, Communication, and Evaluation (BRACE) Special Interest Group (SIG), and the full BRACE SIG was also consulted. The BRACE SIG includes representatives from the pharmaceutical industry, service providers,

academia, and government globally, and was established in August 2012 with the mission to provide an interactive and collaborative forum for education, training, and development among ISPE members with an interest in BRACE. Specifically, BRACE's objectives are: to promote awareness, through education and collaboration, of the intersection of pharmacoepidemiology and BRACE; to define the role, application, and best practices of pharmacoepidemiology to BRACE; and to develop and advance BRACE via:

- development, review and implementation of new tools/methods,
- the development and sharing of applied examples,
- providing a forum for sharing findings and soliciting constructive input from peers, and
- sharing information on best practices and promoting harmonization.

The members of this SIG have unique and relevant expertise on this topic. In addition, several members of the SIG were invited presenters at the FDA workshop on September 18, 2017.

Guidance on Content of the Framework

FDA's structured benefit-risk framework provides a method for FDA to evaluate the available data in a systematic way and make its interpretation of these data and its conclusions explicit. FDA engaged the Eastern Research Group (ERG) to conduct an independent evaluation of the implementation of the framework. Results of the evaluation indicate that a majority of the FDA users of the framework found it helpful in organizing their thinking about a product's benefits and risks in the context of its intended use. Industry drug sponsors also agreed that the framework was a useful tool. Notably, approximately one quarter of FDA staff perceived the main purpose of the framework was to communicate benefit-risk analyses externally rather than to help with internal decision-support. Some users of the framework stated that the framework would benefit from greater consistency in both the level of detail and length of framework reports. In response, the ERG recommended that FDA improve consistency in the level of detail across FDA framework reports and refine the framework template to enhance the way that content is presented. In response to these findings, we request that FDA consider the following recommendations:

1. Recommend that FDA provide guidance on the content, format, and level of detail to be included in the framework.
2. Recommend that FDA encourage sponsors to identify uncertainty in the evidence and provide guidance on how different types and levels of uncertainty should be considered when making benefit-risk determinations.
3. Recommend that FDA work with external stakeholders to provide case studies to show how decision-analytic and patient preference methods could inform benefit-risk assessments, to evaluate the strengths and weaknesses of these methods, and to identify current barriers to including these methods in benefit-risk assessments.
4. Recommend that FDA provide guidance on assessing the effectiveness of risk mitigation activities for identified risks and how this information should be incorporated into post-marketing benefit-risk assessments.
5. Recommend that FDA develop a plan for providing training on the use of the framework for FDA reviewers, industry, patient organizations and other stakeholders.

Guidance on Desirable and/or Useful Patient Input in the Framework

In its PDUFA V implementation plan, FDA noted that the Agency "recognizes that patients have a unique and valuable perspective on these [benefit-risk] considerations and believes that drug development and FDA's review process could benefit from a more systematic and expansive approach to obtaining the patient perspective." To that end, FDA has conducted more than 20 patient-focused drug development (PFDD) meetings. FDA has also indicated its interest in the following topics related to incorporating patient input into the framework: determination of patients' perspective on disease burden and unmet need; and the use of patient preference data in endpoint development, benefit-risk assessments, and post-marketing risk-management programs. We request that FDA consider the following recommendations:

1. Recommend that FDA provide guidance on specific situations in which information on the patient perspective would be most useful or appropriate, including identifying different types of information on the patient perspective and how these different types of information could or should be included in the framework and the extent to which patient-preference information should be used to weight benefits and risks.
2. Recommend that FDA provide direction regarding the stages during the drug review and approval process when patient experience information may impact the FDA's benefit-risk assessments, as well as when these data should be submitted to the FDA for inclusion in such assessments. Additionally, it is important that guidance specify when and how sponsors can consult with the FDA during the pre-submission period regarding the conduct of patient experience and patient preference studies.
3. Recommend that FDA conduct public meetings to solicit input on how patient-focused drug development activities can and should contribute to the framework.
4. Recommend that FDA provide guidance on acceptable ways to elicit and present different types of information related to the patient perspective and provide principles by which studies of patient preferences will be evaluated. In addition, we recommend that FDA increase its internal capacity to evaluate patient experience and patient preference information and encourage industry, patient organizations and other stakeholders to increase their capacity to conduct high-quality patient experience and patient preference studies consistent with these principles.
5. Recommend that FDA provide guidance on when qualitative patient experience information would be acceptable. This may be particularly important in the case of rare diseases with high unmet need where the patient populations are small and quantitative methods are not feasible.
6. Recommend that FDA clarify the boundaries for interactions between sponsors and patients when eliciting patient experience data. We believe that the elicitation of patient input should not be impeded by the important, but addressable, concerns that patient activities designed to understand the patient experience could be considered by the Agency to be promotional in nature.
7. Recommend that FDA provide information about how the Agency may handle certain situations such as when, for example, a pivotal trial fails to demonstrate efficacy on a primary endpoint but is successful in demonstrating efficacy on a secondary endpoint and results of a patient preference study suggest that patients are willing to accept the product's risks in exchange for the benefit captured by the secondary endpoint; or when the results of a patient preference

study show that a defined subset of the patient population is willing to accept the product risks in exchange for the primary endpoint benefit.

Guidance on the Communication of Benefits and Risks

In addition to providing valuable insight into the patient perspective and informing benefit-risk assessment, patient-experience and patient-preference studies will likely provide information that is useful to patients and providers when making treatment decisions. Therefore, we believe it is important that FDA consider the ways in which such information can be communicated to patients, providers, and the general public. We provide the following recommendations related to this topic:

1. Recommend that FDA and sponsors use data visualizations (e.g., the effects table used by the European Medicines Agency) for communicating benefits and risks as part of the framework.
2. Recommend that FDA provide guidance on incorporating patient experience information, including patient-preference information, in product labels.
3. Recommend that FDA consider the possibility of allowing for a separate or additional label that will provide patients with a summary of patient experience and patient preference information developed as part of the drug development process or considered in a benefit-risk assessment.
4. Recommend that FDA provide guidance on the use of patient experience or patient preference information in direct-to-consumer advertising, decision aids, product detailing, and promotional activities including recommendations on acceptable and appropriate ways to communicate such information.
5. Recommend that FDA provide guidance on acceptable and appropriate methods for communicating both benefit and risk information in product labels, direct-to-consumer advertising, decision aids, product details, and promotional activities.