ISSUE BRIEF

Conference on Clinical Cancer Research

November 2011

PANEL 3
Symptom Measurement in Clinical Trials

Ethan Basch, Associate Attending Physician, Memorial Sloan-Kettering Cancer Center
Lori Minasian, Chief, Community Oncology and Prevention Trials Research Group, NCI, NIH
Laurie Burke, Associate Director for Study Endpoints and Labeling, OND, CDER, FDA
Virginia Kwitkowski, Lead Clinical Analyst, FDA
Brian Seal, Director, Health Economics and Outcomes Research, Bayer HealthCare
Mark Gorman, Director of Survivorship Policy, National Coalition for Cancer Survivorship
Richard Levy, Executive Vice President, Chief Drug Development and Medical Officer, Incyte Corp.

I. The value of symptom measurement in oncology

Symptoms are common in patients with cancer, and can be related to disease (e.g., pain from metastatic bone lesions) or to treatment toxicity (e.g., nausea). Symptom burden is a major indicator of disease severity, progression, and improvement. It is a contributor to treatment discontinuation; utilization of medical services; impairment of social, emotional, physical, and professional functioning; decrements in overall quality of life; and long-term morbidity throughout survivorship.

It is therefore essential to understand the impact of cancer treatments on symptoms. Multiple stakeholders require this information to inform their decisions:

- **Patients** trying to understand what to expect with a treatment, based on the prior experiences of their peers.
- **Clinicians** considering treatment options for a particular patient.
- **Sponsors** seeking to understand the benefits and toxicities of a product or dose level.
- **Regulators** balancing benefits vs. risks of a treatment.

Lack of symptom information in contemporary anticancer product labels

Despite the prevalence and importance of symptoms in oncology, rigorously collected information about them is sporadic in pivotal trial data and drug labels. The optimal time to evaluate symptoms is during drug development, because once a product has been approved and marketed for an indication, the opportunity to understand its impact on the patient experience through large randomized controlled trials is largely gone. It is therefore essential for symptoms to be rigorously evaluated during product development in a manner that is amenable to drug labeling and approval.

Regulatory guidance

From a regulatory standpoint, a conclusion of clinical benefit can be based on measurement of the impact of a product on how a patient survives, feels, or functions with respect to their disease in normal daily life. Symptoms affect how patients *feel* and *function*, and symptomatic benefits have served as the basis for approval and labeling of oncology products in the past (1-3).

For example, mitoxantrone was labeled in 1996 as “initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer” based on evidence from two randomized

controlled trials designed to show reduction in pain, although the trials did not demonstrate an overall survival benefit for the therapy (4). Gemcitabine was approved in 1996 for treatment of "patients with locally advanced (nonresectable stage II or stage III) or metastatic (stage IV) adenocarcinoma of the pancreas," in part based on two trials using a composite endpoint comprised of patient-reported analgesic use, pain intensity, performance status, and weight change (5).

However, methodological approaches have evolved over time, and the symptom endpoints used in past clinical trials would not meet contemporary standards in part due to the rigor with which the outcome assessment was developed (adequacy of patient input, validity, reliability, sensitivity, meaningfulness of score changes) as well as to advances in study design and analysis (endpoints models that integrate tumor burden with symptom burden and new approaches to the handling of missing data).

In 2009, the FDA issued the *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (6). This Guidance serves several purposes:

1) It specifies that experiences best known to the patient are ideally assessed using patient-reported outcome (PRO) measures;
2) It demonstrates the FDA's recognition that measures of patient symptoms and patient report of functioning in their daily life represents direct evidence of treatment benefit to support product approval and labeling;
3) It conveys the methodological standards the FDA considers when reviewing trial designs and applications, with the intention of providing general considerations for product developers when using these outcome assessments to define endpoints in trials.

In 2010, an additional FDA Draft *Guidance for Industry: Qualification Process for Drug Development Tools* was issued, providing details of a path for qualification of clinical trial outcome assessments, including PRO assessments, for use as endpoints measures (7).

Sponsor role in symptom measurement

To meet current regulatory guidance, product sponsors generally must begin development of symptom assessments early. During early-phase research, screening questionnaires and patient interviews can identify signals that suggest symptomatic benefits and/or toxicities. Subsequent qualitative and quantitative work in the target population can determine the optimal measurement strategy for focused evaluations in controlled studies, and how PRO measures can support other outcomes in an endpoint model. Then, dedicated PRO measures can be employed systematically in controlled studies to support approval and/or labeling. Early discussion with FDA reviewers is critical to ensure that the role of the symptom assessment is appropriate and that clinical trial results will be interpretable. This will require consideration of the specific context of use so that the clinical trial protocol will optimally define all primary and secondary endpoints needed to make a conclusion about the impact of treatment. In some cases, a symptom endpoint may be a primary endpoint with tumor related endpoints as secondary. In other cases, survival or tumor-related biomarker endpoints may be primary with symptoms endpoints as secondary. Each context must take into consideration not only the inclusion criteria for the planned trials but also the current state of understanding of the disease and the mechanism of action and known toxicities of the drug under development.

Charge to the panel

Despite the clear importance of symptom information to multiple stakeholders and the existing FDA Guidance in this area, there are no contemporary examples of symptom endpoints in anticancer drug labels. This panel was convened to identify the *barriers* to symptoms being included in trials and labels, and to recommend a *path forward* to overcome these barriers. The panel also aimed to identify specific *case studies* of PROs included in recent oncology pivotal trials as primary or key secondary endpoints, and to describe *general scenarios* in which PROs can add value to a clinical development program.

II. Barriers

Several barriers to integrating PROs in trials and labels were identified by the panel, falling into four general categories: 1) *cultural barriers* in industry and the FDA; 2) *communication barriers* between industry sponsors and the FDA; 3) *methodological barriers* to designing rigorous symptom endpoint models in oncology; and 4) *logistical barriers* to implementing these endpoint models in trials.

1. Cultural Barriers

Symptom assessment and PROs are not at the forefronts of the minds of drug developers or FDA oncology reviewers. There is a general preference among both in favor of survival-based, radiographic (tumor size), and serum biomarker endpoints. This preference has evolved historically, during times when survival and treatment options were limited, when scientific research had not yet demonstrated that clinical staff underestimate patient symptoms, and when methods for rigorously evaluating patient-reported information were not yet available. Despite changes in all three of these areas over time, sponsors and regulators remain focused on non-PRO endpoints during drug development. Below, specific cultural barriers, and the infrastructures which sustain them at the sponsor-level and FDA-level, are described:

- **Sponsor-level barriers**: The primary endpoint in oncology is survival, while symptom assessment is important and explored throughout the discovery phase of drug development. There is a trade-off between sponsors' concerns for the need to plan for symptom assessment early in drug development to allow time to develop an assessment tool that is adequately valid and sensitive to treatment effects and the time and expense to complete a trial with a survival benefit to prolong the lives of cancer patients. Symptoms are often not prioritized in clinical development to adequately design or implement an outcome assessment in keeping with the FDA PRO Guidance that provides advice about how to achieve optimal measurement properties to detect treatment benefit signals. Many sponsors believe that the methodological bar set by the PRO Guidance is unrealistically high. The lack of PROs in contemporary oncology labels is cited as evidence that it is difficult or impossible to gain FDA acceptance of these endpoints. Moreover, small companies may lack expertise in health outcomes research or PRO development, while the individuals in large companies who do have content knowledge about PROs may not be part of the clinical development team – they are often in Health Outcomes or similar groups which focus on health-related quality of life assessments across the development cycle. These individuals often feel they are struggling to convince others within companies about the value of PROs. When a PRO measure is included in a study, it is often for an economic evaluation required in Europe (e.g., the EORTC QLQ-C30 or EuroQoL EQ-5D), or a low-on-the-list secondary or exploratory endpoint designed hastily and administered by paper (e.g., a generic HRQL instrument). It is often felt that the expense, logistical inconvenience, and potential delays to clinical development while designing a PRO measurement strategy are not worth the effort. Among drug developers, varying committed resources are allotted to understand the patient subjective experience with treatment; however, rigorous evaluation of PROs starting early in development is the principal method for obtaining approval by the FDA.

- **FDA Barriers**: There does not seem to be an appreciation by FDA regulators that sponsors have been discouraged by the lack of symptom endpoints in contemporary oncology labels, nor a feeling that it is the responsibility of regulators to allay this discouragement. The FDA does not appear to acknowledge that the best way to assure that high-quality symptom information becomes available is to ask sponsors to include rigorous assessment of symptoms throughout product development, starting with early-phase research. Additionally, sponsors would find it beneficial if the FDA provided an assurance that when they proceed with a plan to include a symptom endpoint, communication with FDA will be available to guide development of endpoints that can lead to labeling or approval. During reviews of sponsor materials, it is not standard for FDA reviewers to

consider how information about symptoms or other PROs might enhance understanding of the properties of a given product or support a study design. Similar to industry, the individuals with PRO content expertise are separate from the clinical teams, and are generally only included when the sponsor submits a request for feedback specific to a PRO assessment. Reviewers are variably aware of the methodological considerations related to PROs, despite efforts to provide systematic training and access to consults. There is skepticism about the reliability of measuring patient-reported symptoms due to methodological challenges (described below). There has also been reticence to consider fatigue or health-related quality of life for labeling purposes, in part due to the clinical trial methodological and statistical issues related to multidimensional etiologies. FDA has not provided a means to overcome these barriers although there is research suggesting that these areas are considered important and informative by clinicians and patients.

2. Communication Barriers

Existing mechanisms for communication between sponsors and the FDA include End-of-Phase-II (EOP2) meetings and Special Protocol Assessments (SPAs). These mechanisms generally do not provide an adequate level of exchange for developing symptom endpoints that both meet FDA standards and are feasible for sponsors to implement.

For PRO measures to be compelling, early work with patients in the target population in keeping with regulatory guidance is necessary. By the time there is an EOP2 or SPA, it is often too late to begin such work without delays to a program, and such work often appears overwhelming to sponsors and reviewers who may not have PRO content expertise. Additionally, because of conflicting goals and viewpoints, these exchanges can be more contentious than collaborative: reviewers may not compromise on methodological issues despite feasibility challenges faced by sponsors and sponsors may choose not to meet the high standards set by FDA for PROs, opting instead to drop PROs to lower-level secondary or exploratory endpoints without adequate power. Sponsors often feel that there has not been sufficient specific advice or assurance, and questions are left as "review issues" when FDA is not sufficiently comfortable with an area, leading sponsors to take the most conservative route forward, which often involves dropping PRO endpoints.

Throughout interactions with sponsors, reviewers do not systematically ask whether patient-reported symptoms would enhance understanding of the properties of a product, and they generally do not communicate to sponsors a recommendation to include such assessments in trials. As a result, sponsors come away with a feeling that such assessments are not necessary. Finally, there is inconsistent use of the terms "PROs," "symptoms" and "quality of life" and clarity about what is being measured is essential for communication between sponsors and reviewers.

3. Methodological barriers and solutions

A number of methodological barriers make it challenging to assess PRO endpoints in oncology:

- **Inadequate availability of "off-the-shelf" PRO assessments for use in clinical trials:** Many existing PRO measures were not developed specifically for oncology clinical trials, and may not have been developed or evaluated in keeping with principles of the FDA PRO Guidance. **Solution:** Stakeholders must work together to produce publicly available instruments that will support the detection of treatment impact on how patient feel and function on a tumor-specific basis, in keeping with principles of the FDA PRO Guidance.

- **Inadvertent unblinding related to treatment toxicities**: Many oncology products have unique toxicities that are apparent to patients, and can lead to inadvertent unblinding of treatment allocation. Awareness or suspicion of treatment arm may bias the responses of patients. **Solutions**: Methods for overcoming this challenge include taking measures to retain blinding; requiring a large effect size that

is convincing; and substantiating symptomatic benefits via an association with objective measures (such as radiographic or serum biomarker responses). Research is warranted to assess the extent to which these methods can overcome this source of potential bias.

- **Missing data not at random**: Patients experiencing the most toxicities may feel too ill to self-report, yet assessment of such patients is vital for understanding the full spectrum of the patient experience with a treatment. **Solutions**: Methods for overcoming this challenge include using electronic PRO collection methods that are easy for ill patients to use (such as automated telephone/interactive voice response systems [IVRS]), and employing backup data collection approaches such as a live interviewer who reaches out to patients who don't self-report in real-time. A plan for minimizing missing data and analyzing missing data are essential in any protocol.

- **Concomitant medications**: Many of the symptoms that may be improved with cancer therapy are also treated with supportive medications – such as analgesics for pain; steroids for fatigue; or antiemetics for nausea. **Solutions**: In order to assure that observed benefits on symptoms are related to an anticancer treatment and not to supportive medications, a strategy for up-front optimization and/or for controlling for the use of supportive medications is necessary. Alternatively, evidence that a symptom signal can be detected regardless of use of supportive medications in a given context can be provided.

- **Baseline symptomatology**: Patients with cancer may already have multiple symptoms prior to commencing a trial, related to their cancer, comorbidities, prior cancer treatment, and/or current medications. Therefore, symptom prevalence may ultimately seem higher in both arms. **Solutions**: Methods to overcome this challenge include excluding patients with symptoms of interest attributable to other causes, and/or assessing change from baseline at the patient level.

- **Temptation to use non-PRO symptom measures**: Non-PRO measures cannot substitute for PRO measures when it comes to assessing patient symptoms; for example, the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) is a staff-reporting tool that was not developed as a clinical trial outcome assessment but rather as tool to prospectively monitor adverse events. Experience with this tool has demonstrated empirically that clinicians systematically underestimate patients' symptoms and clinician-generated data should not be used as a substitute for direct patient report of their symptoms. In some situations, surrogates such as family or caregivers may provide data about the patient experience, but this approach requires sufficient supporting evidence of validity and reliability in a given context.

4. Logistical Barriers

Measuring PROs is inconvenient. It takes time, methodological expertise, and direct patient input to develop a measure and endpoint model suitable for U.S. labeling or approval. Within sponsors, internal stakeholders must be convinced that it is worth the effort. Then, experts must assist clinical development teams to make a plan for including PROs. These efforts may be necessary early in development, before it is clear whether a particular product will be moved forward. Then, in a pivotal trial, training of sites and assurance that missing data are minimized is necessary. This work often requires hiring third-party organizations to conduct qualitative research, select or develop a measure, provide ePRO technology, prepare materials for FDA review (e.g., a "PRO Dossier" as specified in the PRO Guidance), and to analyze data. There are limited off-the-shelf measures at this time (although efforts are under way to create them).

III. Case study

A specific case study of an actual drug development program in progress was identified which includes PRO endpoints and ongoing dialog with the FDA. It is described below as an example of how the above barriers have successfully been addressed, and as a model for how mechanisms to better address these barriers can be developed.

Key secondary endpoint supporting a primary radiographic endpoint

- **Disease**: Myelofibrosis
- **Endpoint**: Improvement in six symptoms related to disease
- **Measure**: Simple multi-item questionnaire developed specifically for this trial
- **Administration method**: Handheld electronic device
- **Approach to endpoint development**: Symptoms of interest identified through qualitative work with third-party PRO contractor. Questionnaire developed and refined with direct patient input.
- **Interactions with FDA**: Early face-to-face meeting, SPA
- **Methodological issues**: Large effect size required for responder definition (>50%); only conducted at U.S. sites; very low missing data rate; fatigue not included in measure due to FDA reluctance despite qualitative evidence that this symptom is important to patients
- **Status**: Trial complete, NDA is under review

III. General scenarios where PROs are most informative during product development

The panel identified three general scenarios in which symptom information is most likely to add value to data about a product:

1. A disease with a symptom burden that may be improved by an active anticancer agent

- **Examples**: B symptoms in lymphoma; pain in metastatic prostate or breast cancer; tiredness in metastatic kidney cancer; dyspnea and tiredness in metastatic lung cancer; abdominal bloating/pain in advanced ovarian carcinoma or breast cancer. The National Cancer Institute is interested in developing lists of symptoms pertinent in specific cancer types and a conference focused on this was held in September 2011.
- **Note**: As noted above, screening of patients during early drug development can identify such symptoms and potential improvements in them. Potential study designs include a dedicated symptom study or integration of PROs into a pivotal trial. Such assessments could support approval (either as a primary endpoint supported by evidence of tumor response and lack of survival decrement or as a key secondary endpoint). Symptom improvement alone, without some evidence of anti-tumor effect or survival advantage, would likely not support a regulatory action.

2. A product with similar efficacy but less symptomatic toxicity than an existing product (e.g., comparative tolerability)

- **Examples**: Less peripheral sensory neuropathy than a taxane; less nausea that a platinum-based regimen; less tiredness than interferon.
- **Note**: Demonstrating superior symptomatic tolerability in a non-inferiority trial is appealing to sponsors. As noted above, screening of patients during early drug development can identify when toxicity symptoms associated with a competitor product are not present, and therefore worthy of subsequent systematic comparative evaluation. Notably, evaluation of comparative symptom tolerability requires the same level of rigor as assessment of symptom benefits, and should be in keeping with the FDA PRO Guidance.

3. A trial with a PFS endpoint with OS not likely to be demonstrated due to the long natural history of the condition

- **Examples**: Agents in ovarian cancer or adjuvant breast cancer.
- **Note**: Demonstrating symptomatic benefits may increase the confidence of reviewers in the clinical meaningfulness of PFS results.

IV. Path forward

Several discrete recommendations are proposed by the panel towards overcoming the identified barriers to symptom information being included in U.S. drug labels. These are meant as a starting point for discussion:

1. **Systematically evaluate drug development plans to determine when inclusion of symptom/PRO endpoints are appropriate**
   It should be an FDA expectation that sponsors will provide information about the symptoms experienced by patients during early drug development, with a rationale for why symptoms/PROs should or should not be included as primary or key secondary endpoints in pivotal trials. During EOP2 meetings and SPAs, it should become standard for reviewers to ask sponsors to consider how symptom improvement could enhance the understanding of their product. Such interactions should particularly apply to scenarios described in Section III (above).

2. **Include evaluation of symptoms early and throughout drug development**
   Patients in a target population should be screened by drug developers in early-phase studies in order to detect signals of symptomatic benefits and toxicities. As noted in Recommendation #1, when it is determined that a symptom/PRO primary or key secondary endpoint is appropriate, an endpoint model should be developed to optimally measure these symptoms based on direct input from patients. Next, systematic assessment should be included in pivotal trials, either as a key secondary endpoint to support a survival-based or radiographic-based primary endpoint, or as a primary endpoint in a dedicated study. Inclusion of symptom measures should be particularly emphasized in the three scenarios described in Section III (above).

3. **Improve communication between sponsors and FDA around symptoms/PROs**
   A mechanism should be developed (or an existing mechanism modified) by FDA to encourage an early and ongoing exchange with sponsors to develop a mutually acceptable strategy specifically for including symptoms/PROs in a development program. Such exchanges should be collaborative and open in nature, with a shared goal of identifying methods that are adequately rigorous, yet feasible – and which provide sponsors with assurance that inclusion of PROs can lead to labeling and/or approval. This may require heightened awareness by FDA reviewers about symptom endpoints, or enhanced interactions with internal FDA PRO content experts.

4. **Provide clarity regarding when a dedicated symptom/PRO trial is necessary**
   There should be consistent guidance from the FDA regarding when it is appropriate for a symptom endpoint to be integrated as a key secondary endpoint into a trial with a primary survival-based or radiographic-based endpoint, vs. when a dedicated symptom study is warranted. There should also be clarity about whether full approval of an oncology product could be based on a primary symptom endpoint supported by evidence of tumor response without a decrement in survival.

5. **Identify a path for considering fatigue and health-related quality of life in labels**
   Regulatory research should be commissioned to develop a path for domains related to *fatigue* and *health-related quality of life* to be included in some form in oncology drug labels. These areas are clearly important to patients and clinicians, but have not been considered for labeling because of their complex multidimensional etiologies.

6. **Enhance efforts to develop off-the-shelf symptom and other PRO measures**
   A "PRO Consortium" was created as a part of CPATH to develop pre-qualified PRO approaches in the pre-competitive space. These efforts should be evaluated for barriers to their progress, with recommendations on how to enhance the timely development of measures that meet FDA qualification criteria.

Conclusion

Although it is up to individual companies to make the decision whether to include symptom measures in their development plans, because of the central and authoritative nature of the FDA, it is ultimately their responsibility to actively encourage sponsors to measure symptoms. It is not enough for the FDA to be willing just to consider symptom endpoints. Symptom information must be regarded as essential for understanding the effects of a product, and sponsors should be expected to provide a rationale when such information is not included in a drug development program, rather than the other way around. Impediments to this focus by FDA include significant gaps in clinical trial methodology and outcome assessments. Finally, the FDA must support and enable collaborative interactions with sponsors individually and through consortia towards developing endpoints that are both rigorous and feasible, with assurance that there is a path to labeling.

References

1. US Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007.
2. Rock EP, Kennedy DL, Furness MH, Pierce WF, Pazdur R, Burke LB. Patient-reported outcomes supporting anticancer product approvals. J Clin Oncol. 2007;25(32):5094-9. Epub 2007/11/10. doi: 10.1200/JCO.2007.11.3803. PubMed PMID: 17991927.
3. Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol. 2003;21(7):1404-11. Epub 2003/03/29. PubMed PMID: 12663734.
4. US Food and Drug Administration. Novantrone Drug Label [Last accessed October 10, 2011]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019297s030s031lbl.pdf.
5. US Food and Drug Administration. Gemzar Drug Label [Last accessed October 10, 2011]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020509s033lbl.pdf.
6. US Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Dec 2009.
7. US Food and Drug Administration. Draft Guidance for Industry: Qualification Process for Drug Development Tools. Oct 2010.