Biotechnology Industry Organization

July 30th, 2012

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-D-0432: Draft Guidance for Industry Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval." BIO commends FDA on releasing this Draft Guidance, which will help to develop life-saving medicines for patients with high-risk early-stage breast cancer.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

BIO was pleased to see Agency highlight this particular Guidance in the FDA report on *Driving Biomedical Innovation* (October 2011) as an example of "a relatively seamless pathway that could be followed from a multi-drug screening trial such as I-SPY 2 to an Accelerated Approval" to speed the availability of targeted therapies for breast cancer. BIO appreciates the thought and consideration that FDA has placed into this Guidance and accompanying New England Journal of Medicine article (Prowell & Pazdur, June 2012). In general, the Draft Guidance is helpful and well constructed, providing thorough guidelines on the use of pathologic complete response (pCR) as an endpoint to support Accelerated Approval.

A. BIO Appreciates FDA's Efforts to Develop and Broaden Surrogate Endpoints for Unmet Medical Needs

We hope that FDA considers expanding the use of pCR as a surrogate endpoint to a broader population. Under *the Food and Drug Administration Safety and Innovation Act*

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of 2012 (FDASIA, P.L. 112-144), Congress encouraged FDA to "utilize innovative and flexible approaches to the assessment of products under Accelerated Approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs" and to "establish a program to encourage the development of surrogate and clinical endpoints, including biomarkers, and other scientific methods and tools." (§ *901*) The development of this Draft Guidance is an excellent example of FDA and the scientific community working together in the spirit of collaboration and improved patient outcomes to expedite the development of the next generation of therapies for devastating illnesses. BIO and the biotechnology industry look forward to supporting and contributing to FDA's efforts to identify and develop additional surrogate and intermediate clinical endpoints that can expand the Accelerated Approval pathway to encompass a broader array of life-threatening diseases and conditions.

B. Definition of pCR:

Under the Draft Guidance, "Pathologic complete response (pCR) is defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (*i.e.*, ypT0 ypN0 in the current AJCC staging system)." (lines 154-157)

We agree with this definition of pCR, and agree that residual in situ carcinoma (ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS)) should not be used to judge the efficacy of neoadjuvant therapy. However, we believe the staging criteria for pCR should be ypT0/is ypN0 — not ypT0 ypN0, as is currently stated in the Guidance.

Further, the pCR definition could benefit from additional details or reference(s) that define standards for surgical material, techniques, pathologic sampling methods, etc. Recent efforts to evaluate pCR from I-SPY are conducted in major U.S. centers where these features are fairly well established, so the I-SPY examples likely do not require detailed descriptions, given shared working practices among U.S. surgical oncologists. To enroll larger numbers for disease-free-survival (DFS) / overall survival (OS) endpoints, new sites, including many outside the U.S. will likely need to participate, and the larger number of sites may introduce more variation in working practices, quality, and technical approaches such as time to fixation that can impact marker readout. Thus, more technical details may be of value in this guidance, possibly including specific references from publications designed to improve consistency and quality across multiple treatment centers.[1,2]

C. Additional Considerations should be Evaluated for Ex-U.S. Registration Trials

The I-SPY achievements represent major contributions to academic medicine and demonstrate that experienced U.S. centers could participate in multicenter, randomized

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[1] Hammond ME et al, American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version), Arch Pathol Lab Med. 2010 Jul; 134(7):e48-72;
[2] Hicks DG et al, Breast cancer predictive factor testing: the challenges and importance of standardizing tissue handling. J Natl Cancer Inst Monogr. 2011; 2011(42):43-45)

neoadjuvant protocols to generate efficacy signals by pCR leading to quality publications. A pivotal protocol would likely require expansion by industry Sponsors to include ex-U.S. centers. Thus, the Guidance would likely benefit from additional considerations for marketing approval that may not be sufficiently described in this Draft Guidance.

D. Other "High-Risk" Settings may be Appropriate

Additionally, there is a risk that the document focuses too much on triple-negative disease as the setting in which Accelerated Approval can be contemplated. While we recognize that the draft does indicate "high-risk" disease, it should be emphasized that triple-negative is only an example and that other settings may be appropriate. The data today may not reflect the state of science in five years, so we encourage an appropriate level of flexibility in FDA's guidelines.

E. Interim Analyses may be Appropriate

Finally, the Draft Guidance points out, correctly, that a much larger sample size is required to verify benefit in DFS/OS than pCR. The Draft Guidance suggests a seamless design with one study designed to give both endpoints and no interim analysis of pCR except for a futility analysis. Thus, the Sponsor is required to commit to enrolling the larger sample size without knowing whether the experimental agent is effective based on PCR.

Sponsors may be unwilling to invest in the large trial sample size without supportive clinical data. One large and potentially long study with only a futility analysis provides limited information about the potential benefit/risk profile of the product during, what is essentially, early development. An interim analysis would allow for this.

We suggest the Guidance also allow an initial study (or sub-study) sized for evaluating pCR only, and then either a second study or an expansion of the first to evaluate to DFS/OS if the pCR endpoint is positive.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 36-37:	"Provide guidance regarding trial designs that would permit confirmation of clinical benefit and support conversion to regular approval."	Please clarify whether this approach could be used to support approval of an adjuvant indication once confirmation of clinical benefit in the neoadjuvant setting is obtained.
Lines 48:	"Specific terms and phrases used in this guidance are defined as follows:"	Please clarify if it is the Agency's intent to use the terms "adjuvant" and "postoperative" interchangeably to refer to systemic therapy? If so, please add a definition in this section.
II. BACKGROUND		
A. Rationale for Neoadjuvant Therapy		
Lines 90-96:	"A meta-analysis of approximately 4,000 patients enrolled in 9 trials of neoadjuvant versus adjuvant chemotherapy or endocrine therapy found no evidence that the sequencing of **adjuvant** systemic therapy and surgery alters distant disease recurrence or overall survival (OS) (Mauri et al. 2005). Of note, there was an increased risk of locoregional recurrence in patients who received neoadjuvant therapy compared with those who received **postoperative** adjuvant therapy, which has been attributed to omission of definitive local therapy in some of the neoadjuvant trials (Mauri et al. 2005)."	Please see our comment above at line 48 regarding using "adjuvant" and "postoperative" and edit the text accordingly.

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III. DEFINITION OF PATHOLOGIC COMPLETE RESPONSE		
Lines 154-157:	Under the Draft Guidance, "Pathologic complete response (pCR) is defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (*i.e.*, ypT0 ypN0 in the current AJCC staging system)."	Please see our general comments above.
IV. CLINICAL TRIAL DESIGN AND STATISTICAL CONSIDERATIONS		
B. Trial Designs in the Neoadjuvant Setting		
Lines 248-250:	"It is expected that a large difference in pCR rate between treatment arms will be needed to produce a statistically significant difference in DFS or OS in the overall trial population that is also clinically meaningful."	Please clarify what is considered a "large difference" in pCR rate and how large an improvement would be needed to support Accelerated Approval. In addition, it would be helpful to clarify the definition of "clinically meaningful" differences in the context of this particular Guidance on pCR. Especially since this phrase is used throughout the Draft Guidance.
Lines 277-282:	"This working group, known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC), has embarked upon a large meta-analysis of the relationship between pCR and DFS/OS using primary source data from more than 12,000 patients enrolled in published randomized	Please either include the results of the meta-analysis in the guidance or clarify if there is a pathway to regulatory approval prior to completion of the analysis.

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	neoadjuvant trials with long-term follow-up for DFS or OS available. Important topics that this meta-analysis will address include the correlation between pCR and DFS/OS and the subtypes of early-stage breast cancer in which pCR is most likely to predict clinical benefit."	
Lines 292-311:	"To effectively assess the efficacy of the investigational drug, trials designed to support Accelerated Approval in the neoadjuvant treatment of high-risk early-stage breast cancer should be randomized, controlled trials designed to demonstrate superiority…The analysis should compare pCR rates and DFS or OS between treatment arms, using the full intent-to-treat population."	Industry appreciates and the Draft Guidance makes a notation to "the appropriate magnitude of benefit will depend on the prognosis of the patient population under study and the effectiveness of existing therapy for that patient population". However, industry would find it helpful if the final guidance references the results of the CTNeoBC meta-analysis which may provide some guidance to the magnitude of improvement needed to yield clinical outcomes that are truly meaningful (*i.e.*, DFS and OS) in some breast cancer subtypes.
Line 345:	"Alternatively, clinical benefit may be able to be confirmed in another breast cancer setting."	Please clarify this statement.
Lines 346-347:	"Applicants should plan to collect long-term safety data and provide this to the FDA on an ongoing basis so that serious safety signals can be quickly identified and managed."	Please clarify if this request for long-term safety data is specific to early breast cancer alone?
Lines 357-359:	"All patients should be enrolled in the trial before any efficacy analyses, including analyses of pCR, are performed."	We are concerned about the practicality of this recommendation. While not knowing the success of a drug on pCR, it may be difficult for some investigators and

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		Sponsors to invest resources to continue enroll a large number of patients required to demonstrate DFS/OS. The experimental drug may be effective (based on pCR or other efficacy endpoints from the neoadjuvant trial or other trial(s). While enrolment is still open for DFS/OS, it will be difficult to avoid treatment that could confound results, such as unbalanced drop-off rate from the original neoadjuvant treatment arms.
Lines 366-370	"Because the effect size on DFS or OS is likely to be smaller than the effect size of pCR rate, the statistical analysis plan for controlling the overall false positive rate (type 1 error) for all trial objectives should be structured such that a greater proportion of alpha is allocated to the comparisons of direct measure(s) of clinical benefit (*i.e.*, DFS or OS), and a lesser proportion to the pCR endpoint."	If the final DFS/OS analysis is conditional on achieving a positive pCR analysis, then the alpha may not need to be split for DFS/OS. It would be appropriate to use the early cohort to do a pCR analysis for Accelerated Approval, and then use the completed trial data to conduct the final DFS/OS analysis for regular approval. In this case, the full alpha can be applied with a step down approach to control the overall Type 1 error rate among pCR and DFS/OS analyses.
Lines 377-378:	"...should avoid postoperative cytotoxic therapy intended to treat residual disease found at the time of surgery."	Given the long duration from the diagnosis to the efficacy endpoint, crossover and censoring will become a major issue in assessing DFS/OS. To mitigate this concern, consider using DFS/OS rate at a fixed time-point (landmark) versus the need to wait for mature DFS/OS. The ongoing meta-analyses may be informative if sufficient data are available. The avoidance of cytotoxic therapy may be problematic for physicians and patients, who continue to believe that additional cytotoxic chemotherapy is warranted based on pathologic features or markers that indicate high risk of

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		recurrence, obtained at the time of surgery. Possibly pre-established acceptable post-op treatment regimens for both arms of the trial.
C. Patient Populations for Neoadjuvant Breast Cancer Trials to Support Accelerated Approval		
Lines 413-414:	"What constitutes an appropriate magnitude of benefit depends on the prognosis of the patient population under study and the effectiveness of existing therapy for that patient population."	We suggest adding the safety profile of the combination, in particular with add-on therapy to this list. We also request further guidance on the potential magnitude of benefit that would be acceptable at this time.
Lines 419:	"...high grade, hormone receptor-negative breast cancer (Kuerer et a. 1999; Rouzier et al. 2005)..."	This section describes therapy options for women with high grade, hormone-receptor negative disease. To support alignment between studies and centers, it may be useful to more precisely define high grade, and hormone negative disease including but not limited to acceptable criteria for ER/PR/HER2 positive or negative. For example, the publication by Hammond et al concluded that up to 20% of current IHC determinations of ER and PgR testing worldwide may be inaccurate (false negative or false positive). Most of the issues with testing have occurred because of variation in preanalytic variables, thresholds for positivity, and interpretation criteria. (Hammond ME et al, J Clin Oncol. 2010 Jun 1; 28(16):2784-95). New molecular techniques are emerging in the field of predictive markers including but not limited to new approaches to predict outcomes from adjuvant hormonal therapy (Kim et al, J Clin Oncol. 2011 Nov 1;29(31):4160-7. Epub 2011 Sep 26). As new prognostic markers emerge during the conduct of the neoadjuvant trials, the

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		information can be relevant to understanding outcomes in patient subsets that may not have been pre-specified in the original statistical plan. Further consideration should be given to guide statistical methods or adaptive designs, based on new knowledge of predictive markers that emerge during the conduct of the registration study, prior to the final analyses of clinical outcomes. Examples may include, but are not limited to the following: (1) data from sources external to the registration study, indicating marker(s) predictive of clinical outcomes; or (2) interim analysis of data from the registration study, indicating marker(s) predictive of clinical outcomes. In these or other situations, the Sponsor should be allowed to amend the statistical analysis plan, including sample size adaption and/or analyses to test hypothesis about clinical outcomes in relevant subsets.
Lines 435-436:	"We wish to emphasize that we are concerned about the risk of granting an initial approval in the setting of limited long-term efficacy and safety data from a neoadjuvant trial."	We request guidance on when a drug has additional data or approved indications in other breast cancer settings. Please clarify if this data would alter the regulatory pathway for using pCR in high-risk neoadjuvant breast cancer?
Lines 440-442:	"For all of these reasons, we strongly recommend that patients with hormone receptor-positive tumors lacking high-risk features generally not be enrolled in neoadjuvant trials intended to support Accelerated Approval."	We request that the Agency provide guidance and define the "high-risk features" for patients with hormone receptor-positive breast cancer?

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D. Characterization of Drug Study		
Lines 446-447:	"In a neoadjuvant trial relying upon pCR as the primary endpoint to support Accelerated Approval, long-term safety data will be limited."	We request guidance on how existing safety data in other breast cancer settings may be supplemental to an application based on pCR in the neoadjuvant setting.
Lines 460-465:	"Before designing a randomized neoadjuvant trial, applicants should plan to collect and provide to the FDA at least as much safety data on the investigational drug, alone and in combination, as would currently be needed to launch a phase 3 trial in the metastatic setting. Based on the safety profile and extent of prior clinical experience with the investigational drug(s) or other drugs in the same class, as well as the proposed trial population, additional safety data may be needed to initiate a randomized, neoadjuvant trial with marketing intent."	Please clarify if the Agency expects that the neoadjuvant setting should not be the only treatment setting in which the investigative agent is being studied? Can Investigator-Sponsored studies be included, and rather than only company-Sponsored trials?
Lines 470-472:	"Given these long-term safety considerations, we would emphasize that trials in the neoadjuvant setting should be designed to collect long-term safety data from a number of patients comparable to traditional adjuvant breast cancer trials.	Please state that an open-label safety or observational trial is an acceptable way to collect the data. Please clarify that this could this be done as a post approval commitment.