Biotechnology Industry Organization

October 9, 2015

Steven D. Pearson, MD, MSc, FRCP
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One State Street
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BY ELECTRONIC DELIVERY

RE: Institute for Clinical and Economic Review (ICER) Value Framework

Dear Dr. Pearson:

On behalf of the Biotechnology Industry Organization (BIO), I would like to submit the following feedback with respect to ICER's Value Framework, presented on September 15, 2015.[1] BIO advocates on behalf of biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. In that way, our members' novel therapeutics, vaccines, and diagnostics not only have improved health outcomes, but also have reduced healthcare expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

BIO represents an industry that is devoted to discovering, and ensuring patient access to, innovative treatments. Accordingly, we monitor and engage in discussions around the value of innovative therapies to ensure that patient access and the need to sustain future innovation are appropriately considered by public payors, policymakers, and government regulators. Of principal concern to BIO is that this and any value framework that may be used by such stakeholders: appropriately capture long term benefits of therapeutic interventions; include model inputs that are evidence based; and ensure that the results of the analysis are meaningful to patients, their caregivers, and their healthcare providers. As such, we are keenly interested in ICER's work on the Value Framework and its methodological underpinnings, particularly given ICER's intention to utilize the Framework as the basis for its drug reviews that may be used by public and private payors.[2] As a result, it is important that the Framework employs a reliable and validated methodology, especially since the Framework's outputs will serve as a the primary, or potentially sole, source of information for the public voting process ICER has established to finalize its drug reviews.[3]

In assessing the validity of the Value Framework's methodology, it is instructive to consider how the Framework would assess a therapy that significantly improves upon the standard of care in treating a chronic condition such that it lessens the burden of disease and the need for otherwise-intensive supportive care over the course of decades (e.g., a neurodegenerative disease, such as Alzheimer's disease). The Value Framework would only consider the benefits, costs, and cost offsets in the first five years that the therapy is

[1] ICER. 2015 (15 September). *Evaluating the Value of New Drugs and Devices* [presented via webinar by Steven Pearson, Founder and President, ICER], available at: http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf.
[2] Laura and John Arnold Foundation. 2015. *Press Release: ICER launches new drug assessment program with $5.2 million award from the Lauren and John Arnold Foundation*, available at: http://www.arnoldfoundation.org/icer-launches-new-drug-assessment-program-with-5-2-million-award-from-the-laura-and-john-arnold-foundation/.
[3] See ICER. 2015. Emerging Therapy Assessment and Pricing, available here: http://www.icer-review.org/etap/.

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available on the market. Yet the benefits to patient health outcomes, and in offsetting healthcare system costs over decades, would be ignored. Similarly, the Value Framework would not take into account the therapy's impact on related metrics, like productivity and absenteeism, which are important to patients and their caregivers. As a result, the Framework would find that the hypothetical new therapy is of "low" Care Value and Health System Value, when, if fact, appropriate use of the therapy could not only benefit patient health outcomes but decrease overall healthcare costs and provide important economic, social, and societal value in the longer-term. This is of particular concern for the Medicare program, since the prevalence of chronic conditions is likely to be higher among Medicare beneficiaries than the general population.[4] Any disincentive for the appropriate utilization of a therapy to treat the symptoms of a debilitating chronic disease, like Alzheimer's, slow or stop its progression, or cure it entirely could negatively impact the health outcomes of this population in particular and could result in higher overall costs for the program as whole. Thus, this example highlights fundamental shortcomings in the approach taken by the Value Framework.

In addition to the challenges highlighted by the previous example, the Framework reduces what should be an iterative, informed discussion between stakeholders to the mere consideration of short-term benefits and costs. More concerning still is the potential that this snapshot—which is based on incomplete and/or inaccurate data—will be interpreted and applied inappropriately by public and private payors to inhibit patients' access to therapies that can improve and enhance their lives. Delaying or denying patient access discourages longer-term utilization, which can not only negatively impact health outcomes, but result in missed opportunities to contribute to decreasing overall healthcare expenditures through the avoidance of costly hospitalizations, surgical interventions, physical office visits and other intensive supportive care or medical interventions.

In the following sections of this letter, we identify specific concerns with the methodology the Framework uses to calculate the "Health System Value" metric—given its narrow, short-term-focused scope and its emphasis on an arbitrary average cost threshold—as well as the lack of methodological clarity related to calculating the "Care Value" metric. Unless and until these issues are resolved, BIO urges ICER not to utilize the current iteration of the Value Framework in future drug reviews.

Finally, while the Value Framework's methodology is the focus of this letter, BIO nonetheless would like to take this opportunity to urge ICER to ensure that, moving forward, the development and refinement of the Framework, and the resulting drug reviews, follow a clearly identified process that is inclusive of a broad range of stakeholders.

I. The Value Framework's "Health System Value," as structured, does not consider the comprehensive value an innovative therapy provides to patients and to the healthcare system.

A. <u>The Value Framework's reliance on the quality-adjusted life year (QALY) metric can disadvantage the value assessment of certain types of therapies solely based on how they were studied, not on the value they offer patients.</u>

[4] Bodenheimer, T., E. Chen, and H. D. Bennett. 2009. Confronting The Growing Burden Of Chronic Disease: Can The U.S. Health Care Workforce Do The Job? *Health Affairs* 28(1):64-74.

At its foundation, ICER's assessment of Health System Value—which underlies the value-based price benchmark reported in its drug reviews—relies on a QALY benchmark.[5] As an initial matter, the Institute should identify how it will address the well-documented disadvantages of using QALYs to assess the value of a therapy.[6] For example, since QALYs focus on overall survival, assessments that rely on this metric may inherently attribute a higher value to therapies for which overall survival data are available versus those for which other outcomes (e.g., progression-free survival, response rate) have been the primary endpoints studied. A sole focus on overall survival also can impact clinical trial design, for example, by incentivizing the use of exclusion criteria that prevent the sickest patients from being included in a study or disincentivizing the use of study designs that allow patient cross-over. BIO urges ICER to address these concerns before utilizing the Value Framework in future drug reviews.

B. The Value Framework's "Health System Value" metric does not account for the longer term benefits and cost offsets of biopharmaceutical therapies.

The Value Framework's Health System Value metric also includes a measure of potential budget impact, which is calculated by estimating the net change in total health care costs over an initial 5-year time frame.[7] While we appreciate that the Framework nods to the time-value of a therapy's benefits, BIO is concerned that ICER intends to apply this metric broadly across all therapies, which would inappropriately identify therapies that have substantial costs in the first 5 years, but large cost offsets in later years, as contributing "low" health system value. This is a fundamental challenge for therapies that treat some of the most complex diseases—including chronic diseases like diabetes, cancer, cardiovascular disease, and neurodegenerative conditions, such as Alzheimer's disease—and thus risk being undervalued by ICER's Framework. This metric also overlooks the importance of cumulative innovation, in which innovative therapies alone represent relatively modest clinical benefits, but taken together advance an underlying body of scientific discovery that, in time, results in significant clinical improvements and the advent of cures. Notably, in the event that a curative therapy is developed, this metric would be particularly detrimental to its assessment: as structured, the Value Framework would grossly underestimate the value of a therapy that cures a chronic disease, and thereby eliminates all of the costs to the healthcare system otherwise incurred by decades of chronic treatment. In these examples, a drug review considering such therapies may perversely discourage their uptake based on misinformation, potentially limiting patient access to therapies that could improve their lives.

As these examples illustrate, the time frame over which benefits and costs accrue also may differ based on the therapy, the target population, and the evolving information about the therapy's use. While 10 or 20 years may be an appropriate assessment window for some therapies, others may require even longer assessment time frames to capture the totality of their value. Unless the Health System Value metric is able to reflect the long-term value of a therapy based on the pathophysiology of the disease it treats, the Value Framework will systematically undervalue therapies that are a vast improvement over the standard of care.

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[5] ICER Presentation at 18.

[6] For example, concerns have been raised with regard to: the narrow range of health benefits captured by QALY measurements; testing the theoretical assumptions attributed to the use of QALYs; whether QALYs are the same regardless of to what stakeholder they accrue; equity-weighted utility maximization; and the use of condition-specific measurements in QALY analyses. For additional information, see Whitehead, S. J., and S. Ali. 2010. Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin* 96(5-21); also see Griebsch, I., J. Coast, and J. Brown. 2005. Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. *Pediatrics* 115(5):e600-614.

[7] ICER Presentation at p. 14.

Moreover, ICER's drug reviews are meant to identify and assess therapies that are relatively new-to-market, despite the reality that the understanding of a therapy's benefits and risks, their impact on downstream treatment decisions and broader utilization of healthcare services, and the effectiveness for certain patient subpopulations expands over time. As described in a recently-released white paper on the emerging benefits of oncology therapies over time, "FDA approval marks the 'starting point' for additional study of [a] therapy, followed by the development of a larger body of evidence to help us understand the full value of the treatment and, more importantly, to help clinicians understand how best to use available therapies when treating their patients."[8] Similarly, providers can become more efficient in their use of a therapy over time, which this model would not be able to take into account.

Not only does the Value Framework ignore long-term benefits and cost offsets of biopharmaceutical therapies, but the Framework fails to take into account a therapy's broader benefits to society in the form of decreased mortality and morbidity and improvements in quality of life that can lead to increased productivity and decreased absenteeism for patients and their caregivers. In the absence of taking the totality of a therapy's benefits, and the evolution of these benefits over time, into account, the Value Framework will shortchange the assessment of the therapy's value to patients and to the healthcare system.

C. <u>The Value Framework's use of the term "Health System Value" is inaccurate.</u>

While we understand that the broad purpose of the Value Framework's Health System Value metric is to distinguish a therapy's net costs to the health system from the therapy's net benefits to patient health outcomes, the comprehensiveness implied by the term "Health System Value" is inaccurate. Several significant limitations of this metric are identified in the previous subsection, each underscoring the fact that this metric does not capture the full range of data necessary to assess a therapy's value. Instead, ICER should utilize a narrower term—for example, "health system budget impact"—to help avoid confusion among stakeholders, including providers and patients, who may utilize the Framework to inform their healthcare decision-making process.

II. The Health System Value metric inappropriately compares a cost estimate for an individual therapy to an average cost estimate across all therapies.

The Value Framework's potential budget impact metric relies on a calculation of a cost threshold for individual new drugs. This threshold represents the allowable net additional costs to the healthcare system that a new therapy should impose over the first 5 years on the market (calculated based on the total national health expenditure). The cost threshold plays an important role in ICER's drug reviews insofar as it caps the benchmark price at which ICER concludes a therapy is "valuable" in the health system construct, since, under the Value Framework, a therapy cannot exceed this threshold.[9] ICER has set the cost

[8] Sweeney, N. and T. F. Goss. 2015 (May). The Value of Innovation in Oncology: Recognizing Emerging Benefits Over Time. *Boston Healthcare*, available at: http://www.phrma.org/sites/default/files/pdf/bha_value_of_cancer_innovation-whitepaper.pdf.

[9] If a therapy does not exceed this threshold, the benchmark price is governed by the calculations of the potential price of the therapy pegged to a specific dollar-per-quality-adjusted-life-year measure (e.g., what the therapy would need to cost to be equivalent to $100,000/QALY, or to be equivalent to $150,000/QALY), *see* ICER Presentation pp. 18-19.

threshold at $904 million per new drug by estimating the total amount spent on prescription drugs in 2014 plus an allowable percent increase for 2015 (i.e., gross domestic product (GDP) growth plus 1 percent), and divided that dollar figure by the average number of FDA-approved products per year (i.e., 34).[10] BIO strongly urges ICER to reconsider this methodology since it is established based on averages, and penalizes greater productivity in the research and drug development process and/or the FDA regulatory process.

First, BIO notes the ecological fallacy of comparing the estimate of the short-term budget impact of an individual therapy to an ICER-defined "average" therapy cost to the healthcare system. The Value Framework suggests that a comparison of the individual estimate to the average estimate provides information about the former, when in fact it does not. Different therapies contribute differently to the healthcare system based on a number of factors, including but not limited to, the underlying disease burden that a therapy targets, whether it treats the symptoms or cause of the disease, the number of patients for whom it is appropriate, and the aggregate impact on individual patients' lives. Other factors that should be considered include the delivery of care, site of service, and type of provider. In fact, comparing an individual therapy to a broad average will inherently disadvantage certain types of therapies. For example, therapies that treat large populations may be assigned to the "low" health system value category—regardless of their potential benefits—because of their broad utilization. In turn, if such a snapshot were applied to coverage and reimbursement decisions, patient access to such a therapy could be limited, negatively impacting short- and long-term patient health outcomes and contributing to a climate that disincentivizes research and development in therapies to treat large patient populations.

Second, BIO calls into question the methodology for calculating the cost threshold. For example, the rationale ICER provides for tying the cost threshold to GDP growth is inapt: the Affordable Care Act's Independent Payment Advisory Board (IPAB) is required to consider broad categories of healthcare costs, while the Value Framework looks at only a small piece of healthcare costs. Moreover, tying the cost threshold to an average number of FDA approvals will perversely penalize improved efficiencies in the FDA process that serve to bring therapies to market faster (i.e., as the number of newly approved drugs increases, the denominator for the cost threshold increases, and the cost threshold applied to an individual drug decreases). Based on these concerns, BIO strongly urges ICER to reconsider this metric to build in the nuances associated with an individual drug's impact on the healthcare system and to foster an environment that encourages, not discourages, more efficient drug development for patients.

III. The data on which the Health System Value metric is based should be evidence-based, and where possible, accurately reflect the realities of the marketplace.

To calculate Health System Value, ICER relies on, among other components: the price of the therapy; an estimate of the "unmanaged" uptake of new drugs; and an assessment of the associated cost offsets. The information underlying these estimates is inaccurate and the assumptions are not sufficiently evidence based, and thus are likely to bias the assessment of the value of the most innovative therapies. The methodology should be revised before utilizing the Value Framework as the basis for any future drug reviews.

First, ICER utilizes a therapy's wholesale acquisition cost (WAC) when comparing the "price" of the drug to the ICER-calculated benchmark. This is problematic because WAC does not

[10] Id. at p. 12, 15-16.

reflect the discounts and rebates that are widely negotiated in the marketplace. Moreover, ICER does not appear to use the same metric for all drug reviews: the review targeting PCSK9 inhibitors, released in September 2015, utilizes WAC, whereas the review targeting the management of congestive heart failure, released the same week, utilizes WAC minus a calculated discount, rather than just WAC. Thus, not only is ICER inconsistently utilizing this metric of a therapy's price, but the metric itself misrepresents the therapy's actual cost.

Second, ICER notes that broad assumptions regarding the unmanaged uptake of new drugs are made in assigning a therapy to one of the four identified uptake patterns, and subsequently, for calculating the therapy's budget impact. Based on this methodology, the size of the available patient population will drive the calculation of potential budget impact. However, it is unclear how ICER intends to estimate unmanaged utilization, particularly in newly approved drugs that are commonly subject to utilization management controls. To maintain consistency and predictability, ICER must estimate potential utilization based only on a therapy's FDA-approved label. FDA employs a robust, evidence-based review in determining for which patient populations a therapy is appropriate, information that is included in the product label at the time of approval. Moreover, since ICER has identified an interest in assessing therapies shortly after they are available on the market—i.e., before real-world data on utilization are available—the label information is the most reliable source of information.

In this same regard, BIO also asks ICER to clarify whether and how the Institute intends to update the inputs of the Value Framework in response to changes in the market, such as increased competition from a newly-approved therapy, or the release of updated data, such as data not initially available at launch that provide information on longer-term outcomes. The Framework is particularly sensitive to changes in these inputs, and thus ICER should address how it will reflect the most up-to-date information or how it will identify the Framework's limitations brought about by failing to do so.

Third, since the potential budget impact metric is net of cost offsets, how such offsets associated with a specific therapy are calculated is crucial to the accuracy of the metric. However, the methodology for calculating cost offsets is not detailed in the Value Framework. Thus, before applying the Value Framework to future drug reviews, ICER should publish its methodology for calculating cost offsets and seek stakeholder input on that framework. One issue, in particular, that ICER should address is whether and how stakeholders outside of those participating in the formal ICER process can submit data and how ICER will consider and incorporate such information. ICER also should address how it will contend with cases in which a therapy's FDA-approved indications target significantly different patient populations, resulting in different benefit and cost-offset considerations.

IV. The Value Framework's methodology for calculating Care Value requires additional clarity before being employed for additional drug reviews.

Additionally, ICER must clarify two aspects of the Care Value measure before moving forward with the Value Framework in future drug reviews to afford stakeholders an opportunity to understand how this measure is calculated. First, ICER should provide additional details around how the different components of Care Value—comparative clinical effectiveness, incremental cost per outcomes achieved, other benefits or disadvantages, and contextual considerations—are calculated and/or weighted. While ICER does note that "the relative importance of 'other benefits or disadvantages' in an overall determination of Care Value will be judged not by ICER but by one of its independent public appraisal committees," the Institute does not go further to identify how this independent assessment

will impact or be integrated with an assessment of the other Care Value components.[11] A better understanding of how the measure is calculated is important to provide clarity for stakeholders attempting to interpret ICER's findings appropriately.

Second, though ICER has noted that a therapy's Care Value is assigned to one of three categories (i.e., high, intermediate, and low), the Institute has not commented on the specific boundaries of these categories, the transition points between categories, and/or whether such broad categories are capable of capturing the nuances of treatment advancements in all therapeutic areas and how each of these evolve over time. While individual drug reviews do provide greater detail with regard to the Care Value category to which a therapy is assigned, stakeholders would benefit from a better understanding of the standards that ICER uses to apply this categorization scheme in the first place. This detail informs stakeholders' perspective on the strengths and/or limitations of utilizing the Value Framework to assess different types of treatments. For example, depending on how the boundaries are set for each category, the Value Framework may be more or less capable of capturing the nuances of treatment advances for diseases/conditions with heterogeneous, versus homogeneous, patient populations (e.g., smaller changes in the Care Value components may be required to move a therapy's assessment from "low" to "intermediate" depending on the features of the patient population targeted by a specific therapy). Thus, ICER should provide this additional insight before utilizing the framework in future drug reviews.

V. Conclusion

BIO reiterates our principal concern that the Value Framework is not appropriate for assessing the long-term value of innovative therapies, instead providing only a snapshot in time of a therapy's benefits and costs. As such, ICER should address these fundamental concerns before utilizing the Value Framework in its drug reviews. BIO looks forward to additional opportunities to contribute to ICER's ongoing work, and continues to encourage the Institute to provide more information on, and opportunities for stakeholder input into, its process for developing and refining the Value Framework and the drug reviews that utilize it. Please feel free to contact me at (202) 962-9200 if you have any questions or if we can be of further assistance. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

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[11] ICER Presentation at p. 9.