

May 4, 2016

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**RE: Follow-Up on BIO's Comments in Response to the ICER Value Framework**

Dear Dr. Pearson:

The Biotechnology Innovation Organization (BIO) would like to take the opportunity to follow-up and expand on the feedback we originally submitted to the Institute for Clinical and Economic Review (ICER) in October 2015 on the ICER Value Framework (the "Framework").<sup>1</sup> BIO is the world's largest trade association representing 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.

In the fall of 2015, ICER released the Framework that is meant to underlie the ICER Drug Assessment Program reviews (the "Reviews") to be conducted over the next several years.<sup>2</sup> In response, BIO submitted written comments that expressed concerns that certain aspects of the Framework's methodology may unfairly bias ICER's value assessment of innovative therapies, in turn, contributing to the restriction of, rather than facilitating, patient access to needed therapies. In the course of the last several months, BIO has had the opportunity to review the application of the Framework in several specific Reviews. We submit this letter in follow-up based on this recent experience and with the hope that ICER will adopt an inclusive, stakeholder-driven process to consider and implement refinements to the Value Framework to ensure it better represents the comprehensive value that innovative therapies offer patients, the healthcare system, and society as a whole.

As a general note, BIO remains concerned that aspects of ICER's Value Framework methodology—coupled with the Reviews' focus on pricing thresholds to establish Provisional Health System Value and cost effectiveness—does not align with the Institute's broader goal of assessing medicines' "true value to patients."<sup>3</sup> We understand that ICER intends to refine the use of this metric in the Review process moving forward, and while we appreciate the Institute's willingness to reconsider how this metric is utilized, our original concerns with the methodology used to calculate it nonetheless persist.<sup>4</sup> Specifically, in our original feedback,

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<sup>1</sup> 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>.

<sup>2</sup> 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/>.

<sup>3</sup> *Id.*

<sup>4</sup> Section 6.5 of ICER's most recent Review notes that "[v]alue-based price benchmarks will be provided as part of the full Evidence Report." See ICER. 2016 (April 7). *Treatment Options for Relapsed or Refractory Multiple*

BIO focused on providing recommendations specific to each aspect of the Value Framework in the hope that this would make it easier for ICER to refine the Framework in the context of its existing structure. However, in the intervening months, as BIO has considered value assessment tools developed by other third-party organizations, several important themes have emerged, including:

- The meaningfulness of the metrics used to assess value;
- The specificity and reproducibility of the methodology used to calculate value;
- Whether the methodology accounts for the benefits and risks of a healthcare intervention to a patient over the course of his/her disease and promotes individualized care;
- Whether the methodology adequately accounts for the value of innovative therapies;
- Whether the value assessment tool establishes a mechanism to be updated based on the evolving standard of care; and
- The inclusiveness and responsiveness of the tool to diverse stakeholder input.

Throughout the remainder of the letter, BIO expands on these concerns and provides specific examples from existing Reviews. For example, we have serious concerns with regard to the meaningfulness of the quality-adjusted life year (QALY) metric utilized by the Framework's "Care Value" metric, as well as its potential to disadvantage the assessment of a therapy's benefits based solely on how those benefits are measured (e.g., overall survival versus other primary endpoint). Similarly, we express concern that ICER's application of an identical budget impact threshold for every new molecular entity in the "Provisional Health System Value" metric cannot accurately capture the value of innovations that significantly impact the standard of care. These, and other, examples are discussed in more detail throughout this letter.

In providing this feedback, BIO is not offering specific comments on any individual Review or assessment of any individual therapy, but rather, we are referencing several final Reviews to demonstrate that the application of the Framework does not comprehensively take into account the value of innovative therapies, and thereby applying it in the context of the Reviews shortchanges the assessment of the value of biopharmaceutical therapies. Though we understand that ICER may be planning to discuss changes to the Framework in a forum to be held in September 2016, the persistent concerns with the Framework warrant a cessation of its application to ICER Reviews until such a time as these concerns can be adequately addressed.<sup>5</sup>

## **I. General Categories of Concern with regard to the Value Framework and its Application to the ICER Reviews.**

The six themes identified in the introduction are critical to a value assessment tool's ability to facilitate patient access to high quality care. In fact, these themes identify a higher-order rubric for determining whether such a tool is structured to meet this primary goal. Applying this rubric to the Framework illustrates several fundamental, structural issues that BIO urges ICER to address as an initial step to refining the Framework. Each structural issue that is identified in this section is discussed in more detail in the balance of this letter.

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Myeloma: Effectiveness and Value (Draft Report). Section 6.5, p. 55, available at: [http://icer-review.org/wp-content/uploads/2016/04/MWCEPAC\\_MM\\_Draft\\_Evidence\\_Report\\_040716.pdf](http://icer-review.org/wp-content/uploads/2016/04/MWCEPAC_MM_Draft_Evidence_Report_040716.pdf).

<sup>5</sup> ICER. 2016 (March 17). *ICER Membership Methods Advisory Group Meeting Summary*.

The meaningfulness of the metrics used to assess value: ICER's Provisional Health System Value metric—a key aspect of the Value Framework's output and the focus of individual Reviews—is based, in part, on trends in national economic performance and an estimate of the total number of new drugs approved for marketing per year: two metrics that are wholly unconnected to the value of a therapy to patients, caregivers, or society as a whole, leaving the patient perspective largely absent from the Framework. In fact, the patient perspective is largely absent from the Value Framework. Moreover, this metric is not structured to adequately measure value given the short timeframe over which it considers the benefits, costs, and cost offsets of a therapy. As ICER applies the Framework to the Reviews, the issue of meaningfulness is compounded as the timeline on which the Reviews are conducted (i.e., soon after the availability of a new therapy on the market) necessarily means that much of the real-world evidence of a therapy's use is not yet available.

This is of specific concern with respect to refractory disease settings, including but not limited to, oncology. At launch, surrogate endpoint data (e.g., response rate) may be the only data that is known about therapies that treat these types of conditions. Therefore, the clinical benefits known at launch may not reflect the comprehensive value of the therapy to patients.<sup>6</sup> The timing of ICER's Drug Reviews, and the lack of a process to update the reviews as new evidence emerges (discussed in greater detail below), results in the exclusion of more comprehensive data on aspects of treatment that may be most meaningful to patients—including a more complete portrait of the impact on short-, intermediate-, and long-term health outcomes and quality of life.

The specificity and reproducibility of the methodology used to calculate value: BIO remains concerned that ICER is still unclear with regard to identifying the data inputs for, and the relative weights assigned to, each component of the Care Value measure. There is also a general lack of specificity and clarity with regard to the assumptions on which the Framework's economic modelling components rely. Moreover, the assumptions used to calculate product uptake, for purposes of assessing budget impact, can be unrealistic, significantly distorting estimates of the cost of a new therapy. The lack of clarity with regard to exactly what assumptions, models, and calculations are utilized to arrive at an output metric is detrimental to the ability of stakeholders to understand the limitations and relevance of review findings in real-world settings.

Whether the methodology accounts for the benefits and risks of a healthcare intervention to a patient over the course of his/her disease and promotes individualized care: BIO continues to express concern with regard to ICER's continued use of only a 5-year measurement window to assess budget impact (i.e., Provisional Health System Value). This is especially true since ICER has, and continues to, target chronic conditions for its Reviews, including rare diseases. These conditions manifest over multiple years or even decades, and can have a differential impact of patients depending on their personal (including genetic) characteristics. Especially in the case of rare diseases, this impact can be challenging to study given the size of the patient population. Thus, the 5-year assessment window and the metrics of "average" value, which are not unique to individual patient experiences are, inadequate to capture the full range of benefits, costs, and cost offsets of an innovative therapy to individual patients, the healthcare system, and society. If ICER does not revise this aspect of the Framework's methodology, the Institute may contribute to stifling the innovation ecosystem by systematically undervaluing therapies that have relatively high

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<sup>6</sup> For a more detailed discussion of this issue, see (for example): Institute of Medicine. 2009. *Assessing and Improving Value in Cancer Care*. National Academies Press, available at: <http://www.ncbi.nlm.nih.gov/books/NBK219551/>.

upfront costs but represent significant improvements in the standard of care and can improve longer-term patient health outcomes and decrease longer-term healthcare system expenditures. Additionally, as noted above, the timing of the Reviews—soon after the FDA approval of a new therapy—necessarily limits the availability of data describing the impact of a therapy on patient subpopulations, which is critical information that can promote individualized clinical decision making.

Whether the methodology adequately accounts for the value of innovative therapies: BIO remains concerned that the Framework does not adequately account for the impact of innovative therapies on patients' lives, including improvements to their ability return to their daily routines, and on society as a whole, including through improvements to worker productivity, and the broader cost offsets of a healthier population. In part, this is due to the short timeframe over which a therapy's "budget impact" is assessed and the timing of the ICER assessment itself (as described above), and the Framework's inability to take into account other stakeholders' views on the quantitative and qualitative value of innovation. ICER's Value Framework also excludes consideration of the impact of cumulative innovation, in which, over the course of decades, seemingly small, distinct advancements in the standard of care accrue to substantial improvements over time (e.g., consider the case of chronic myelogenous leukemia, for which the 10-year survival rate increased from 20 percent a decade ago to 80 percent today).<sup>7</sup> In fact, as expressed by many of the points that are raised in this letter, the term "Provisional Health System Value" is misleading since the methodologies utilized by the Framework do not encompass an assessment of the broader patient and societal impact of a therapy. Instead, ICER should rename this metric the "Budget Impact" metric, to more appropriately identify the purpose and findings of this aspect of the ICER assessment.

Whether the value assessment tool establishes a mechanism to be updated based on the evolving standard of care: Though BIO understands that ICER's intention with the advent of the Review process is to review new-to-market therapies, we are concerned that these reviews are conducted in the absence of a full picture of a therapy's benefits and disadvantages (discussed in detail in a later section) and that these reviews will continue to be relied upon by other stakeholders even after additional data (e.g., real-world evidence) emerge. Thus, we ask ICER to provide a more comprehensive description of the limits of the Framework and the Review process such that the potential utility of each is well characterized. This will help to prevent either from being applied out of context, potentially to the detriment of patient access to needed therapies. Additionally, ICER should consider establishing a formal process for updating the Framework, and the Reviews that rely on it, in the event that novel data becomes available for analysis after an initial Review has been finalized.

The inclusiveness and responsiveness of the tool to diverse stakeholder input: BIO remains concerned that the lack of a formal comment period after the release of the Framework, paired with the often short timelines for response to an individual Draft Review, results in a lack of meaningful opportunities for stakeholder input. We appreciate the recognition of similar issues at the March 17 meeting of the ICER Membership Methods Advisory Group.<sup>8</sup> BIO believes that the detailed comment timeline, proposed as a solution to these concerns at that meeting, while helpful, is not sufficient to address this issue. Instead, ICER must consider an amended approach to public engagement. Inclusiveness is critical to

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<sup>7</sup> Yin, W. et. al. 2012. Value of Survival Gains in Chronic Myeloid Leukemia. *American Journal of Managed Care* 18(11):S257-S264.

<sup>8</sup> ICER. 2016 (March 17). *ICER Membership Methods Advisory Group Meeting Summary*.

ensure that ICER can obtain and consider information to which it may not otherwise have access, as well as gain an understanding of the practical impact of the Reviews on various stakeholder groups.

Patients' input, in particular, is important to ensure that any value assessment tools is patient-centered. The National Health Council, in establishing a Patient Centered Value Model Rubric, noted that, to have true utility, a value assessment tool must have "robust processes in place to incorporate the patient voice," a perspective with which BIO is in complete accord.<sup>9</sup> In the absence of broad stakeholder input, and engagement with patients in particular, ICER is shortchanging the assessment of the value of innovative therapies to the detriment of those who may reference ICER's work. Moreover, the lack of stakeholder engagement may similarly impact ICER's other value initiatives. For example, ICER's White Paper entitled *Indication-specific Pricing of Pharmaceuticals in the U.S. Health Care System* was developed with limited input from only certain stakeholder groups.<sup>10</sup> While the document catalogs challenges to indication-specific pricing, it does not address critical issues around the impact of this type of value-based arrangement on patient care and on providers in the short-term, and on the ecosystem that supports biopharmaceutical innovation in the longer term. Thus, to better ensure that the Institute's work broadly reflects a range of issues and perspectives, BIO urges ICER to engage in an inclusive, iterative feedback process with stakeholders across its value initiatives moving forward.

## **II. The Value Framework's components, as structured, do not capture the comprehensive value an innovative therapy provides to patients and to the healthcare system.**

In BIO's original comments, we noted concern that the Framework's "Care Value" metric relies on QALYs, which are arbitrary and do not holistically assess the value of a therapy to an individual patient. As an initial matter, we reiterate that ICER has yet to address the well-documented disadvantages of using QALYs to assess the value of a therapy.<sup>11</sup> 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 (though we recognize that QALYs can take into account quality of life associated with other outcomes, such as progression-free survival, response rate, albeit with varied weight). Moreover, a preference for the overall survival metric can favor therapies studied through clinical trials with restrictive inclusion/exclusion criteria that may prevent the sickest patients from participating in the study or incentivize the use of study designs that do not allow patient cross-over. Yet paradoxically, ICER appears to consider the inclusion/exclusion criteria of the trials assessed as part of the Review process, and raises concerns with regard to the limitations of such criteria in identifying "controversies and uncertainties."<sup>12</sup> BIO urges ICER to address concerns with the use of QALYs before

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<sup>9</sup> National Health Council. 2016 (March). *The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric*, available at: <http://www.nationalhealthcouncil.org/sites/default/files/Value-Rubric.pdf>.

<sup>10</sup> ICER. 2016 (March 15). *Indication-specific Pricing of Pharmaceuticals in The U.S. Health Care System: A Report from the 2015 ICER Membership Policy Summit*, available at: <http://www.icer-review.org/icer-releases-white-paper-isp/>.

<sup>11</sup> 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.

<sup>12</sup> For example, ICER's Drug Assessment Review of therapies treating congestive heart failure noted in the "Controversies and Uncertainties" section that "[a]nother critique relates to the fact that the pivotal trial was

moving forward with the application of the Framework to future Reviews. In doing so, ICER should consider the potential to utilize alternative mechanisms to assess Care Value—including long-term projections/modeling estimates of clinical outcomes that are more inclusive than overall survival, and considering long-term survival and other assessments of long-term patient health benefits.

BIO's original comments also identified significant concerns with the fact that the Framework's "Provisional Health System Value" metric does not account for the longer term benefits and cost offsets of biopharmaceutical therapies. This issue persists as one of BIO's primary concerns given that ICER continues to utilize only a 5-year assessment window for assessing Provisional Health System Value, and employs estimates of utilization and patient adherence rates that do not reflect clinical realities. Moreover, this concern is exacerbated by the fact that ICER continues to target chronic diseases as the subject of future Reviews.<sup>13</sup> The 5-year timeframe for assessment is inappropriate for these conditions, in particular, given that they manifest over much longer time periods. Thus, treatments that meaningfully improve upon the standard of care in these therapeutic areas are disadvantaged in the Review process because the majority of their benefits will occur outside of the assessment window.

**III. The Provisional Health System Value metric is not calculated in a standardized manner, and its structure and application in the ICER Reviews can threaten patient access and negatively impact incentives for biopharmaceutical innovation over the long term.**

- A. Utilization, in the context of the Provisional Health System Value metric, is assessed inconsistently and biases Reviews against therapies that treat large patient populations.

As an initial matter, in our original engagement with ICER, BIO urged the Institute to estimate potential utilization based only on a therapy's Food and Drug Administration (FDA)-approved label. We made this recommendation based on two factors: first, 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. However, most, but not all, Reviews mention that utilization was calculated assuming an uptake pattern for the therapies in question if covered for the FDA-labeled indications.<sup>14</sup> Second, 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. However, it is unclear what standard ICER uses in each Review.

BIO's original consideration of the Provisional Health System Value metric also identified the concern that the metric is structured to compare an individual therapy to a

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conducted only among patients who tolerated a "run-in" phase of treatment." See California Technology Assessment Forum (CTAF). 2015 (December 1). *CardioMEMS™ HF System (St. Jude Medical, Inc.) and Sacubitril/Valsartan (Entresto™, Novartis AG) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks*. p. ES13, available at: [http://ctaf.org/sites/default/files/u148/CHF\\_Final\\_Report\\_120115.pdf](http://ctaf.org/sites/default/files/u148/CHF_Final_Report_120115.pdf)

<sup>13</sup> ICER identifies the following chronic diseases as areas of interest for review in 2016: primary biliary cirrhosis, Duchenne muscular dystrophy, non-small cell lung cancer, multiple sclerosis, and psoriasis and psoriatic arthritis. See ICER. 2015 (November 19). ICER Announces Initial List of Topics for 2016 New Drug Reports on Effectiveness, Value, and Value-Based Price Benchmarks, available at: <http://www.icer-review.org/icer-announces-initial-list-of-topics-for-2016-new-drug-reports-on-effectiveness-value-and-value-based-price-benchmarks/>.

<sup>14</sup> Note: Such a statement is not included in the Review assessing therapies that treat congestive heart failure.

broad average. This can inherently disadvantage patient access to certain types of therapies if a Review is utilized in making coverage, formulary, or reimbursement decisions as it appears is ICER's intent. For example, therapies that treat large populations may be assigned to the "low" Provisional Health System Value Category—regardless of their potential benefits to patients—because of their broad utilization. In fact, Provisional Health System Value appears to be significantly driven by ICER's estimate of likely utilization in the first 5 years. For example, ICER estimated low utilization for therapies assessed in the Reviews of severe asthma with eosinophilia and diabetes. In both cases, this utilization estimate contributed to preventing the Price Benchmarks from exceeding ICER's \$904 million budget threshold.<sup>15,16</sup> However, ICER estimated very high utilization for therapies assessed in the Reviews of congestive heart failure and high cholesterol. This utilization, in turn, contributed to therapies in both of these Reviews exceeding the ICER budget threshold, which triggered the "cap" on the Price Benchmark.<sup>17</sup> This bias against therapies that treat large patient populations appears to exist regardless of the value such medicines may have to individual patients and the healthcare system. Ultimately, such a bias can support inefficient, inappropriate healthcare choices, by discouraging the utilization of medicines that may offer significant health benefits, and diminish investment in treatments and cures for large patient populations, resulting in missed opportunities to help reduce overall health expenditures.

Finally, BIO asks ICER to provide context with regard to whether and how the Institute considered the utility of internationally-accepted research standards for determining short-term budget impact, given that ICER's current methodology does not entirely align with such international norms. For example, the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR's) has identified *Principles of Good Practice for Budget Impact Analysis*.<sup>18</sup> Yet ICER does not appear to refer to these guidelines, and does not follow several aspects of the identified methodology. For example, ICER's estimate of the uptake of a new therapy appears to be at direct odds with the international standard established by ISPOR:

"Specifying who is included in this population [utilizing the therapy] is not straightforward. It depends, of course, on the approved indication but it also reflects local intended restrictions on use (and reimbursement), possible off-label or beyond-restriction use, induced demand (i.e., the proportion of previously untreated patients who now seek treatment because of improved outcomes, greater convenience, or fewer side-effects), and the extent to which practitioners adopt the technology or change patterns of use of existing ones. The budget impact model must be designed

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<sup>15</sup> (CTAF). 2016 (March 14). *Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks*, available at:

[http://ctaf.org/sites/default/files/assessments/CTAF\\_Mepolizumab\\_Final\\_Report\\_031416\\_0.pdf](http://ctaf.org/sites/default/files/assessments/CTAF_Mepolizumab_Final_Report_031416_0.pdf);

CTAF. 2016 (March 14). *Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks*, available at:

[http://ctaf.org/sites/default/files/assessments/CTAF\\_Degludec\\_Final\\_Report\\_031416\\_0.pdf](http://ctaf.org/sites/default/files/assessments/CTAF_Degludec_Final_Report_031416_0.pdf).

<sup>16</sup> This is relevant because, for therapies that do exceed this threshold, the Price Benchmark is capped in relation to the threshold itself, and no longer based on ICER's cost per QALY assessment (note: BIO has serious concerns with ICER's reliance on QALYs, explained in detail in an earlier section of these comments).

<sup>17</sup> CTAF. 2015 (December 1). *CardioMEMS™ HF System (St. Jude Medical, Inc.) and Sacubitril/Valsartan (Entresto™, Novartis AG) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks*, available at: [http://ctaf.org/sites/default/files/u148/CHF\\_Final\\_Report\\_120115.pdf](http://ctaf.org/sites/default/files/u148/CHF_Final_Report_120115.pdf); CTAF. 2016 (November 24). *PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and ValueBased Price Benchmarks*, available at: <http://cepac.icer-review.org/wp-content/uploads/2015/04/Final-Report-for-Posting-11-24-15.pdf>.

<sup>18</sup> ISPOR. *Principles of Good Practice for Budget Impact Analysis*, available at: [http://www.ispor.org/workpaper/BudgetImpactAnalysis/BIA\\_TF0906.asp](http://www.ispor.org/workpaper/BudgetImpactAnalysis/BIA_TF0906.asp).

to allow for examination of the effect of alternative assumptions about the nature and size of the treated population.”<sup>19</sup>

BIO notes that this description of ISPOR’s methodology points specifically to the need to take into account restrictions on utilization, yet ICER assumes just the opposite (i.e., its Review calculations are made based on unmanaged utilization). Not only does this deviate from international standards, but in the U.S., this assumption is not supported by evidence that suggests that, payers can impose utilization management restrictions on over 70 percent of therapies that treat certain diseases/conditions in certain segments of the insurer market.<sup>20</sup> Thus, stakeholders would benefit from greater insight and clarity into the assumptions on which ICER’s budget impact analysis is built, especially in comparison to other types of analyses in use and the realities of the U.S. marketplace, in order to be able to make specific recommendations with regard to how to refine it.

It is also unclear why ICER takes a “health system perspective” in establishing cost-effectiveness models in some Reviews (e.g., the Review assessing high cholesterol therapies) but takes a payer perspective in others (e.g., the Review assessing severe asthma with eosinophilia therapies). The perspective ICER assumes is important because it dictates the inclusiveness of the cost offsets that ICER considers, which, in turn, impacts the Price Benchmark. Specifically, the health system perspective considers all direct and induced medical costs and relevant clinical outcomes, while the payer perspective focuses on direct health care costs only, and only for the population enrolled in a given benefit structure. These inconsistencies make it difficult to interpret the findings of the ICER reviews in the context of clinical care and real-world utilization.

**B. The Provisional Health System Value metric’s reliance on Wholesale Acquisition Cost (WAC) is inappropriate and misleading.**

One of BIO’s primary concerns with the structure of the Provisional Health System Value metric is that it continues to utilize 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 reflect the discounts and rebates that are widely negotiated in the marketplace, and thus is misleading with regard to the “cost” of the therapy to any individual patient. Moreover, ICER does not appear to use the same metric for all drug reviews. For example, the Review of therapies treating high cholesterol and severe asthma with eosinophilia utilized WAC, while the Review of therapies treating congestive heart failure utilized WAC minus a calculated discount, and it is unclear what measure was utilized by the Review of therapies treating diabetes (ICER lists “annual drug costs” simply as “calculated”).<sup>21</sup> In the absence of a consistent and transparent measure of cost to different stakeholders, including to patients individually, the Framework is missing a critical element of the calculation of value.

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<sup>19</sup> ISPOR. *Principles of Good Practice for Budget Impact Analysis*. “Population,” available at: [http://www.ispor.org/workpaper/BudgetImpactAnalysis/BIA\\_TF0906.asp](http://www.ispor.org/workpaper/BudgetImpactAnalysis/BIA_TF0906.asp).

<sup>20</sup> Avalere Health. 2014 (March 24). Consumers Face More Hurdles to Accessing Drugs in Exchange Plans Compared to Employer Coverage, available at: <http://avalere.com/expertise/life-sciences/insights/more-controls-on-drug-access-in-exchanges>.

<sup>21</sup> CTAF. 2016 (March 14). *Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks*. Table 7, p. 30, available at: [http://ctaf.org/sites/default/files/assessments/CTAF\\_Degludec\\_Final\\_Report\\_031416\\_0.pdf](http://ctaf.org/sites/default/files/assessments/CTAF_Degludec_Final_Report_031416_0.pdf).

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

In our initial communication, BIO asked for clarification on two issues in particular: first, 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 or whether any of these components take into account patients’ perspectives of the value of specific therapies. Moreover, to assess comparative value, ICER constructs a simulation model of outcomes and costs. For certain Reviews (e.g., Reviews assessing therapies that treat diabetes) the model that is utilized is robustly sourced, while in others, the model is based on a much smaller body of evidence, introducing greater uncertainty around the assumptions on which the model is based (e.g., in the case of the Review of severe asthma with eosinophilia therapies, the model is based on a cost-effectiveness model of a different therapy). In the latter circumstance, it is unclear whether, or if, the sensitivity analyses conducted are sufficient to capture the robustness of the model itself. The assumptions that ICER makes in modeling comparative value underlie the final value assessment and heavily influence the Price Benchmark. Thus, understanding the limitations of the model is critical to understanding the limitations of the Review.

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 issues will evolve over time. For example, in the Review assessing therapies that treat high cholesterol, the California Technology Assessment Forum (CTAF) was asked to assess the Care Value of the new therapy over standard of care based on existing evidence. The vote margin between “intermediate” and “low” was only two votes. Moreover, we understand that review panels may not always receive the same instructions with regard to how they should utilize the voting algorithm (e.g., simply as a guide rather than a strict framework). ICER also has indicated a change in voting instructions to the Forums moving forward.<sup>22</sup> Thus, unless ICER specifically defines these categories and institutes a clear, standardized understanding of how panelists approach voting (and factors that may change that recommended approach), these vote can be seen as arbitrary and not reproducible. This lends uncertainty to the utility of the eventual value assessment of the Review.

Though BIO originally requested additional details on these two aspects of the Framework, in particular, we never received a response, contributing to our concerns voiced throughout this letter that ICER has not established a meaningful process for obtaining and considering stakeholder input. While ICER publishes responses to comments received during the open comment period on an individual Draft Review, there is no such process in place for ICER to receive and respond to stakeholders’ comments on the underlying Framework methodology itself. Thus, in addition to our comments recommending that ICER establish such a process, we ask ICER to include a public response to comments received as an integral part of such a process as well ((e.g., organizations such as the European network for Health Technology Assessment (EUnetHTA), and other groups, seek to utilize a

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<sup>22</sup> ICER. 2016 (April 7). Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value (Draft Report). Section 6.5, p. 55, available at: [http://icer-review.org/wp-content/uploads/2016/04/MWCEPAC\\_MM\\_Draft\\_Evidence\\_Report\\_040716.pdf](http://icer-review.org/wp-content/uploads/2016/04/MWCEPAC_MM_Draft_Evidence_Report_040716.pdf).

transparent process to identify if and how the organization has responded to public comments received).

D. The data on which the Provisional Health System Value metric is based should be comprehensive and patient-centered.

In several cases, ICER notes that research relevant to the assessment of the value of a therapy is ongoing, and thus, cannot be included in a current Review. BIO appreciates that ICER identifies such limitations with these analyses, but questions whether it is reasonable to have gone forward with the Review in the absence of such critical information. For example, in the Review assessing therapies that treat severe asthma with eosinophilia, ICER recognizes the importance of studies that follow patients over a longer timeframe, and notes that “[t]here are open-label extension studies of both trials [used for the ICER analysis] (see Appendix E) that are following patients for up to 3.5 years, but no published data are available as of yet.”<sup>23</sup> Additionally, we note that IMS Health research shows that multiple stakeholders—including integrated delivery networks, managed care organizations, and pharmacy benefit management organizations—increasingly rely on real-world evidence to make utilization decisions with regard to medicines.<sup>24</sup> Thus, in the absence of an evidence-based explanation of why ICER would move forward with a Review prior to the availability of additionally data describing the real-world use of biopharmaceutical therapies, we find ICER’s rush to judge these therapies incongruous with a thoughtful, comprehensive analysis of their value.

E. If the Provisional Health System Value metric informs coverage and reimbursement determinations, patient access to appropriate therapies can be threatened.

The inconsistencies in measuring Provisional Health System Value aside, BIO remains very concerned that if this metric, in the context of its inclusion in an ICER Review, is applied to coverage and reimbursement decisions, patient access may suffer. The limited time period over which ICER has chosen to measure the health system value of a therapy, as well as the lack of assessment of value from the patient perspective, risks undervaluing an innovative therapy that offers significant clinical benefit over the standard of care. If such a skewed metric informs coverage and reimbursement determinations, patient access to appropriate therapies can be inappropriately limited, which will negatively impact patient health outcomes and detract from the broader societal benefits reaped from improvements in patients’ health.<sup>25</sup> Furthermore, ICER’s population-level assessments should not be misused in ways that impede providers and patients from tailoring evidence-based decisions to the needs and preferences of the individual. Given the methodological concerns expressed throughout this letter, the Framework also can negatively impact the incentives in the broader ecosystem to invest in research and development for therapies that treat large patient populations.

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<sup>23</sup> CTAf). 2016 (March 14). *Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and ValueBased Price Benchmarks*. p. 16, available at: [http://ctaf.org/sites/default/files/assessments/CTAF\\_Mepolizumab\\_Final\\_Report\\_031416\\_0.pdf](http://ctaf.org/sites/default/files/assessments/CTAF_Mepolizumab_Final_Report_031416_0.pdf).

<sup>24</sup> IMS Health. 2015 (May). *Why pharma needs to work differently with payers and IDNs on RWE: Learnings from recent survey and symposium*. Figure 2: Payer and IDN use of RWE today, p. 4, available at: [http://www.imshealth.com/files/web/Global/RWE/RWE-Collateral/RWE\\_white\\_paper\\_IDNs\\_and\\_Payers.pdf](http://www.imshealth.com/files/web/Global/RWE/RWE-Collateral/RWE_white_paper_IDNs_and_Payers.pdf).

<sup>25</sup> For example, see Grabowski, D. C., D. N. Lakdawalla, D. P. Goldman, M. Eber, L. Z. Liu, T. Abdelgawad, A. Kuznik, M. E. Chernew, and T. Philipson. 2012. The Large Social Value Resulting From Use Of Statins Warrants Steps To Improve Adherence And Broaden Treatment. *Health Affairs* 31(10): 2276-2285; also see Philipson, T. J., and A. B. Jena. 2005. Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs. *National Bureau of Economic Research (NBER) Working Paper No. 11810*.

Similarly, we raise concerns that tying the cost threshold, as the Provisional Health System Value metric does, to an average number of FDA approvals benchmarked against the U.S.'s gross domestic product (GDP) is an arbitrary standard. This methodology 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). Additionally, applying an identical threshold for each new molecular entity does not capture the value of a therapy to patients, their caretakers, or society as a whole, especially for disease or conditions with a high prevalence.

#### **IV. Conclusion**

BIO reiterates our principal concern that the Framework does not assess the long-term value of innovative therapies, and is insufficient to account for the perspectives of a diverse group of stakeholders on the value of innovative therapies. Instead, the Framework provides only a snapshot in time of a therapy's benefits and costs. Thus, we continue to urge ICER to address these fundamental concerns before utilizing the Framework in future Reviews. BIO looks forward to 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 processes. 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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