Biotechnology Innovation Organization

April 3, 2017

Steven D. Pearson, M.D., M.Sc. FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

BY ELECTRONIC DELIVERY

RE: National Call for Proposed Improvements to its Value Assessment Framework

Dear Dr. Pearson:

The Biotechnology Innovation Organization (BIO) appreciates the opportunity to provide feedback in response to the Institute for Clinical and Economic Review's (ICER's) Call for Comments on Revised Value Assessment Framework (the "Value Framework").[1] 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.

BIO appreciates that ICER has provided an additional opportunity for stakeholder comment in advance of finalizing revisions to the Value Framework. While some of the proposed revisions have the potential to make progress toward aligning the Framework with the principles of individualized patient care and holistic value assessment, ICER must provide additional details with regard to how these proposed revisions will be operationalized before stakeholders can assess whether the revisions will meaningfully address critical gaps in the Framework.

However, we remain concerned that the proposed revisions to the Value Framework do not address the central concerns that many stakeholders raised during the initial comment period. Specifically, even with the proposed revisions, the Value Framework would still:

- Inappropriately conflate the impact of a therapy on patient health outcomes, including quality of life, with the potential budget impact to any individual payer or group of payers;

[1] ICER, 2017 (February 1), *Institute for Clinical and Economic Review Posts Revised Value Assessment Framework for Public Comment*, available at: https://icer-review.org/announcements/vaf-revision-public-comment/ (last accessed February 28, 2017).

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

- Fail to uniformly rely on robust and validated methodological standards, and apply them consistently and transparently; and
- Fall short of fulfilling ICER's stated goal of "fairly reward[ing] innovators for the value they bring to patients, and provide them ample incentive to pursue the investments and research that will lead to the innovative treatments of tomorrow."[2]

The balance of this letter will provide feedback that is intended to align the Value Framework with established research methodologies and standards for analytic robustness and accuracy. BIO's recommendations on ICER's proposed revisions fall into two broad categories: (1) those revisions that require additional detail, and potentially even operationalization, to determine whether they are wholly responsive to BIO's recommendations; and (2) critical issues that ICER did not address—or did not address adequately—in the proposed revisions. We urge the Institute to work collaboratively with a diverse range of stakeholders, including manufacturers and patients, to revise the Value Framework further to promote patient-centered healthcare and incentivize biopharmaceutical innovation over the longer term.

While our recommendations throughout this letter are made with specific reference to the Value Framework, we urge ICER to apply our recommendations in the context of the Institute's broader work as feasible. For example, we recognize that ICER is studying certain types of therapies, including gene therapies and medicines that treat patients with rare diseases, outside of the existing Drug Review and Value Framework process. We believe this approach is appropriate given the unique issues associated with these types of therapies. In particular, BIO appreciates that ICER has acknowledged that the revised Value Framework will not apply wholesale to ultra-orphan disease therapies due to considerations around clinical trial design and evidence, size of the potential patient population, differences in demands of research and development, and the need to weigh other benefits and disadvantages and contextual considerations. That said, we nonetheless strongly urge ICER to ensure that its other initiatives employ robust and transparent analyses, are patient-centric, and do not underestimate the value of innovative new therapies.

I. BIO urges ICER to provide additional details with regard to several of the proposed revisions such that stakeholders can better assess whether these proposals will meaningfully address gaps in the Framework identified during the original comment period.

A. Estimating Net Price

ICER proposes to utilize an estimate of the net price of prescription drugs in the value assessment methodology rather than relying on the Wholesale Acquisition Cost (WAC), or list price. While ICER has provided high-level detail with regard to the data used to make net price assumptions, it remains unclear how the assumptions are applied differentially across different types of therapies in a single Drug Review, and how the assumptions are applied across Drug Reviews. As just one example of the need for additional clarity, we note that it is unclear

[2] ICER, 2016, *Addressing the Myths About ICER and Value Assessment*, p. 2, available at: http://icer-review.org/wp-content/uploads/2016/08/icer_myths_facts.pdf (last accessed August 31, 2016).

whether and how ICER may take into account the loss of exclusivity of innovative biopharmaceuticals in its economic evaluations. This market reality has a significant impact on the cost, over the long term, of an innovative therapy, and that impact has been well documented.[3] If ICER does not take this into account, the Institute should clarity the rationale behind this decision.

Moreover, BIO agrees that using "net price" is advantageous compared to considering only a therapy's list price, so that rebates and discounts often available in the marketplace can be taken into account. However, the benefits of this approach rely on the accuracy of the estimate of net price. Thus, stakeholders will be unable to judge the impact of moving from a list- to a net-price estimate unless there is a more predictable, transparent framework in place to understand how these estimates are calculated.

B. Estimating New Therapy Uptake

ICER proposes to cease assuming "unmanaged utilization" in Drug Reviews that include a new therapy, and instead take into account the slower rate of utilization often seen with new-to-market therapies. BIO agrees with this proposed revision. In implementing it, we urge ICER to: (1) make the process for generating assumption inputs, and the assumptions themselves, transparent to stakeholders; (2) base the assumptions on existing evidence and realistic scenarios (e.g., the use of utilization management techniques by payers), and clearly identify for stakeholders the evidence on which these assumptions are made; (3) engage recognized clinical experts and experts within the industry throughout the process to lend real-world expertise and experience to the analysis and calculations; and (4) apply the underlying methodology for making uptake assumptions consistently within and across Drug Reviews. In addition to using historical data, we note that the estimation of new treatment uptake can also consider evidence-based treatment guidelines, especially where there is a change in the treatment paradigm, as well as any other quality of care measures that may impact prescribing behavior.

BIO recognizes that the process for generating uptake assumptions will be distinct for therapies that have been on the market for some time compared to those that may be newer to market. This distinction, and its inherent impact on the uptake assumptions, is a key rationale for engaging experts with real-world experience and expertise throughout the process of generating uptake inputs. For example, in ICER's reviews of rheumatoid arthritis, multiple sclerosis, and non-small cell lung cancer, many of the therapies included had been available to patients for several years. In cases such as these, it is relatively straightforward to analyze healthcare claims data to make conservative market uptake assumptions. However, in practice, it appeared that ICER's assumptions were not closely tethered to these real-world observations, which can risk the public's misperception of actual utilization and does not serve to inform payers with regard to potential budget impact (short or long term). Thus, we urge ICER to ensure that future reviews employ the above recommendations with regard to uptake assumptions.

---

[3] IMS Institute for Healthcare Informatics, 2016 (January), *Price Declines after Branded Medicines Lose Exclusivity in the U.S.*, available at: https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/PhRMA%20Generic%20Price%20Brief%20January%202016.pdf (last accessed March 31, 2017).

Furthermore, BIO continues to raise significant concerns with the inclusion of therapies in Drug Reviews before sufficient real-world evidence is available (see section III for a detailed discussion of BIO's concerns). However, if ICER continues to do so, we urge the Institute to ensure that the uncertainty around uptake assumptions for a new-to-market therapy, versus therapies that have been on the market for a while and thus their use is more easily characterized, does not inherently bias a Review against the new therapy.

C. Stakeholder Engagement

BIO appreciates ICER's proposed commitment to engage more directly with stakeholders, including patients, in future Drug Reviews. However, ICER must provide additional details with regard to how this commitment will be operationalized before stakeholders can assess the impact of the proposed revisions on meaningful public engagement. For example, we note that while ICER has stated a commitment to incorporating the patient perspective to a greater degree into individual Drug Reviews, several patient advocacy organizations have noted that ICER's use of the information these groups have provided is not consistent and their role is not formal. As the Institute works to refine and improve its engagement mechanisms, ICER should consider looking to FDA's approach to Patient Prioritized Endpoints (PPE) as an example. Specifically, the Agency plans not only to obtain patient perspectives first hand through formal meetings, but will develop a formal mechanism to evaluate patient insights and prioritize patient insights in the approval of medicines that address PPE.

In considering ICER's proposed revisions further, we recognize that the Institute often notes the Public Advisory Councils (PACs) as a cornerstone ICER's stakeholder engagement. However, the Value Framework revisions do little to address the need to improve the transparency around the PACs and the process by which they PA are incorporated into Drug Reviews. As a threshold matter, we urge ICER to clearly identify the criteria used to choose PAC members and to consider whether it is appropriate to provide foundational training on comparative effectiveness assessment and other relevant topics for those PAC members who do not have an expertise in these areas (e.g., those appointed based on clinical expertise or those serving as patient representatives). Additionally, ICER should ensure that these Councils are briefed well in advance of their public meetings so that they are able to guide well-informed discussion during such meetings and vote based on a thorough review of the evidence provided and understanding of patients' clinical experiences.

BIO also continues to urge ICER to incorporate the patient perspective more diligently into the PACs moving forward. While we appreciate ICER's 2016 announcement of the appointment of a patient advocate to the ICER Governance Board, this does not replace the need for true subject matter expertise—including with respect to patients' perspectives—on the Councils themselves.[4] At a minimum, ICER should include at least one to two patients or patient advocates, referred by credible patient advocacy organizations, with expertise in the

[4] ICER, 2016 (July 21), *ICER Elects Patient and Consumer Advocacy Experts to Governance Board*, available at: https://icer-review.org/announcements/icer-gov-board/ (last accessed July 22, 2016).

disease/clinical condition at issue in each Drug Review. ICER could do this in a number of ways, including following the examples of the National Comprehensive Cancer Network (NCCN), Patient-centered Outcomes Research Institute (PCORI), or Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), described later in this subsection.

Similar to our concern with regard to the inclusion of patients on PACs, BIO continues to express strong concern that ICER does not include a sufficient breadth of clinicians on the PACs who have expertise in the disease area currently under study on their health technology assessment bodies. Especially in the case of chronic, complex conditions, those with expertise in the clinical treatment of patients are the most abreast of rapid evolutions in the standard of care and the nuance of making individualized clinical decisions. Not only should subject matter experts be involved in vetting the comparative clinical effectiveness questions that a Drug Review identifies (discussed above, see Section I), but it is important that they have a role in reviewing and validating the model inputs in any clinical and cost-effectiveness analyses. The inclusion of clinical experts on the HTA organizations that ultimately review the Framework's application and vote on the renamed "Long-Term Value for Money" metric will also improve ICER's ability to update drug reviews based on emerging evidence.

There are several models ICER can emulate to address these recommendations regarding expanding the representativeness of the PACs. For example, NCCN establishes individual panels of clinicians and researchers that share a specific expertise to develop and update the NCCN Guidelines for oncology care.[5] These experts utilize their clinical expertise and existing evidence to make recommendations, and routinely update these recommendations based on emerging evidence. A similar example can be found in the statutory requirement PCORI establish expert advisory panels to consult on the funding of research that is related to rare diseases and clinical trials.[6] In fact, the inclusion of a requirement for subject matter expertise as a statutory provision demonstrates that this is a standard with regard to comparative clinical effectiveness. Moreover, PCORI maintains a particularly robust standard for patient engagement, extending the role of patients to involve them at the time a research question is defined and requires patients to have an active (vs. consultative) role in the governance, operations, interpretation, and dissemination of research. Given that PCORI's approach to patient-centered research has been developed over a period of years in concert with experts in clinical and non-clinical research, we strongly urge ICER to use it as a model for patient engagement moving forward.

Yet another example is MEDCAC, which maintains a pool of up to 100 experts in various fields and, from that advisory group, chooses "no more than 15 members with

---

[5] National Comprehensive Cancer Network, *About the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*, available at: https://www.nccn.org/professionals/default.aspx (last accessed on August 22, 2016).

[6] See ACA § 6301(d)(4). It is worthwhile to note that, while statute only identifies the topics of "clinical trials" and "rare disease" as the subject of required PCORI expert advisory panels, it permits the formation of others, and PCORI has established 7 such panels on the following subjects: assessment of prevention, diagnosis, and treatment options; improving healthcare systems; addressing disparities; patient engagement; clinical trials; rare disease; and communication and dissemination research. See PCORI, 2016 (June), *Join an Advisory Panel*, available at: http://www.pcori.org/get-involved/join-advisory-panel (last accessed September 1, 2016).

knowledge specific to the topic in question to serve on the panel for each MEDCAC meeting."[7] MEDCAC also has an established mechanism to "recruit non-MEDCAC members who have relevant expertise to provide additional input to panel members and invite experts to make formal presentations to the MEDCAC for a particular meeting."[8] While BIO has raised issues with MEDCAC's application of the model in practice in the past, the general structure of their process can serve as an example nonetheless.[9] No matter how ICER decides to implement this recommendation, we strongly urge the Institute to ensure that reviews are targeted to the appropriate patient population based on evidence-based treatment guidelines and the FDA-approved label, and to do so immediately such that ongoing reviews benefit from the participation of subject matter experts.

Finally, we recognize that the public comment processes associated with individual Drug Reviews are an important element of stakeholder engagement. However, while ICER has made progress in refining these processes to allow for the participation of a broader range of stakeholders, we continue to urge the Institute to establish minimum public comment periods of at least 30 days—for draft scoping documents—and 60 days—for more dense documents like the draft evidence review. These are recognized standards for public comment periods, and shorter timelines effectively exclude critical stakeholder perspectives, such as patient advocacy organizations (e.g., many of which do not have the resources to respond under shorter deadlines).

D. Transparency of the Value Framework Methodology and Data Calculations

BIO appreciates ICER's interest in making the Value Framework's methodology and calculations more transparent, including the underlying rationale and evidence that support these. However, until this is operationalized in the context of a Drug Review, it will be difficult for stakeholders to assess if the level of transparency ICER provides is sufficient to allow reproducibility of its results. At a minimum, we urge ICER to finalize this commitment and state that it will include transparency with regard to the following:

- The exact methodology used in the network meta-analysis (NMA) and comparative effectiveness analysis (CEA);
- The clinical rationale for all of the modeling assumptions; and
- The full details regarding the results (e.g., model fit statistics for all models assessed).

Additionally, it remains unclear whether the broader transparency described in the proposed revisions will apply to the following aspects of ICER's process, all in need of additional clarity: (1) the process for choosing therapeutic areas/clinical indications to study and obtaining input from clinical experts; (2) which stakeholders ICER engages in the development of a Draft Scoping Document and how the feedback received is taken into account, including

---

[7] Centers for Medicare and Medicaid Services (CMS), 2016, *Medicare Evidence Development & Coverage Advisory Committee*, available at: https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html.
[8] Id.
[9] BIO, 2014 (August 29), *Comments in Response to the Proposed Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) Charter*, available at: https://www.bio.org/advocacy/letters/bio-submits-comments-hhs-regarding-proposed-medicare-evidence-development-and-cover (last accessed April 1, 2017).

documentation of why certain considerations are not applied; and (3) the timeline and notification process for posting detailed model analysis plans. Thus, BIO urges ICER to work internally and with stakeholders to ensure that the additional transparency discussed in the proposed revisions document definitively extends to each of these three areas before proceeding with any additional Drug Reviews.

As a means of facilitating meaningful transparency in the context of individual Drug Reviews, BIO urges ICER to make their modeling assumptions and the analytical model itself easily accessible to all stakeholders to facilitate independent validation. This requires that the models not only be complete when they are posted, but that they are available in a timely manner such that comments on their underlying analysis can be made in the context of comments to the Draft Evidence Reports.

E. Incorporation of "Additional Benefits and Disadvantages" and "Contextual Considerations" into the Value Framework

ICER proposes to implement the BIO recommendation to more deliberately and systematically incorporate the information in the "additional benefits and disadvantages" and "contextual considerations" categories into the Value Framework methodology. However, until this is operationalized, it will be difficult for stakeholders to assess whether this proposal, once finalized, will lead to a more patient-centered assessment of innovative biopharmaceuticals and other medical technologies.

ICER specifically proposes to adopt a modified form of multi-criteria decision analysis (MCDA) that will "delineate the[se] elements and use a weighting system to integrate their consideration as part of long-term value for money." In doing so, BIO urges the Institute to identify any evidence to support their proposed modified MCDA methodology. We also urge ICER to ensure that this modified MCDA methodology should not be used to identify a cost-effectiveness threshold, due to high subjectivity associated with the proposed weighting exercise and a lack of evidence validating the approach. ICER also should clearly identify how the MCDA will take into account various patient population characteristics, especially in the case of small or particularly vulnerable patient populations (e.g., pediatric, sociodemographic patient subpopulations, rare diseases). Moreover, we continue to raise concerns with ICER's reliance on the subjectivity of the appraisal committees to make final rankings of the categories of "additional benefits and disadvantages" assessed, which is not a scientifically or statistically robust process.

While BIO supports the incorporation of a broad range of evidence in any assessment of value, we continue to be concerned that the Value Framework does not take steps to ensure that assessments that include breakthrough therapies do not inherently undervalue the clinical advances these therapies make. Specifically, therapies that have been on the market longer—and thus have more data available for analysis—may be at an advantage compared to newer-to-market therapies. This is particularly the case for therapies approved through FDA accelerated approval pathways, which will not have the same breadth of data available as do those that have been on the market for a longer period of time. Any value framework must identify and

implement mechanisms to take into account this natural asymmetry in available data and ensure that assessments of breakthrough therapies accurately recognize the positive impact the therapy can have on patients and the healthcare system.

Finally, with regard to quantitatively incorporating the "contextual considerations" category in particular, BIO urges ICER to consider the societal perspective on the benefits and costs of innovation, including indirect costs of productivity loss and caregiver burden. In particular, we urge ICER to incorporate the impact of cumulative innovation into this category moving forward.[10] Cumulative innovation describes the concept that relatively modest improvements in patient outcomes that result from individual innovative therapies build on each other to advance the scientific field forward, and result in major advancements on the standard of care over time. Each individual advance is important to the overall improvement in treatment for these patients. For example, the cancer death rate has fallen by 20 percent since 1991, in large part due to medicines.[11] The survival rate among children with cancer is approximately 83 percent compared to 58 percent in the mid-1970s. Yet, despite this reality, the ICER Framework does not take into account cumulative innovation, and thus, can shortchange the value of innovative therapies to the detriment of patient access in the short term and continued innovation over the longer term.

F. Greater Use of Sensitivity Analyses

BIO agrees with ICER's proposal to incorporate additional sensitivity analyses into assessments relying on the Value Framework methodology, but we recognize the numerous qualifications the Institute includes in discussing this proposed revision (e.g., "as possible[,]" "as relevant"). We urge ICER to provide additional details with regard to the specific circumstances under which the Institute will consider including these analyses in a Drug Review (e.g., what data need to be available, whether such analyses are dependent on certain features of the patient population or disease/condition). Additionally, we urge ICER to identify how these sensitivity analyses will be incorporated into the Value Framework's summary metrics to ensure that the context such analyses provide filters up to the information that is highlighted as the "result" of a given Drug Review.

G. Updates to Previous Drug Reviews based on Emerging Data

ICER has acknowledged the need to consider updating previously-conducted Drug Reviews based on updated or emerging evidence. BIO had previously identified concerns with the static nature of the Value Framework, which continues to only capture a snapshot of time. However, to assess whether ICER's proposal to consider updating previous reviews goes far

---

[10] Cumulative innovation describes the concept that relatively modest improvements in patient outcomes that result from individual innovative therapies build on each other to advance the scientific field, and result in major advancements on the standard of care over time. Each individual advance is important to the overall improvement in treatment for these patients.

[11] PhRMA, 2014 (May 14), *Five Facts About the Value of Innovative Cancer Medicines*, available at: http://catalyst.phrma.org/five-facts-about-the-value-of-innovative-cancer-medicines (last accessed September 12, 2016).

enough to counterbalancing the inherent disadvantage of the current "snapshot-in-time" approach, ICER must provide additional details with regard to the following:

- How ICER will track emerging evidence on therapies that were previously evaluated by the Value Framework;
- The minimum level of evidence that must exist for ICER to consider updating a previous Review;
- Any additional criteria that ICER will require to consider updating a previous Review;
- Whether the update will include updates to the net price and utilization assumptions specifically;
- ICER's process for updating a previous Review, including notification to stakeholders and stakeholder engagement; and
- Whether the update will be comprehensive or only target certain aspects of the previous Review (and if the latter, which aspects will be updated).

We recognize that, on March 20, ICER announced its intent to produce a "New Evidence Update" to its 2015 review of the comparative clinical effectiveness and value of PCSK9 inhibitors.[12] While we appreciate that ICER is already operationalizing this proposed revision to the Drug Review process, the press release does not answer the questions we pose with regard to the detailed process for identifying and conducting New Evidence Updates (e.g., whether the update will include real-world effectiveness and post-approval safety data). Thus, we urge ICER to proactively establish a standardized process for updating Drug Reviews to provide predictability for stakeholders moving forward.

II. BIO is disappointed the ICER largely ignored recommendations that would have practically addressed the Value Framework's inappropriate conflation of value, short-term affordability, and budget impact.

BIO recognizes that ICER revised the conceptual framework underlying the Value Framework to respond to stakeholder concerns that the Value Framework did not distinguish between the distinct assessments of value, short-term affordability, and budget impact. However, the proposed conceptual revisions were not reflected in the actual Value Framework methodology, which maintains a budget impact threshold in the context of a value-based price benchmark, and continues to rely on the same flawed, overly simplistic summary metrics. Our significant concern with this approach is that it can mislead policymakers and other stakeholders to believe that arbitrary spending caps can improve patient care and stem healthcare costs, when in fact *the opposite* is true: research has clearly demonstrated the negative impact of such caps on patient access to needed medicines, incentives for future innovation, and market efficiency,[13] as

[12] ICER, 2017 (March 20), *Institute for Clinical and Economic Review to Produce "New Evidence Update" Including Updated Value-based Price Benchmarks for PCSK9 Inhibitors to Treat High Cholesterol*, available at: https://icer-review.org/announcements/pcsk9-new-evidence-update/ (last accessed March 21, 2017).

[13] For example, see Ciarametaro, M., S. Abedi, A. Sohn, C. Fan Ge, N. Odedara, and R. Dubois. 2017. Concerns Around Budget Impact Thresholds: Not All drugs are the same. *Value Health* 20(2):230-233. See also Thomas A. A., and J. A. Wernon. 2007. The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions. *MDE Managerial and Decision Economics* 28:293-306.

well as the potential of such policies to lead to higher overall healthcare costs (e.g., from increased hospitalizations, emergency department visits, surgical interventions, and physician office visits).[14] BIO reiterates our concerns with the application of this aspect of the Value Framework in the remainder of this section.

A. Short-Term Affordability Metric

Though ICER proposes to rename the provisional health system value metric to "short-term affordability," BIO recommends further revision so that the terminology used more accurately characterizes the output of the metric. Given that "affordability" is a subjective term and can have different meanings to different stakeholders, we urge ICER to rename this metric the "short-term payer budget impact" measure. Given ICER's perspective from the point of view of a health system payer, renaming this metric to clearly identify that perspective would help to avoid any confusion among the various audiences for Drug Reviews.

In considering ICER's proposed revisions, we note that while the Institute proposes to rename this metric, ICER does not propose to alter the fundamental elements of the metric, and thus, does not address BIO's core concerns with this metric and its application. Specifically, BIO continues to be concerned that this metric only takes into account a 5-year time horizon. As such, we do not believe it is meaningful in the context of clinical care, especially for the chronic conditions ICER continues to target for Drug Reviews. These diseases—and the therapies that treat them—impact patients over the course of a decade or longer, which is the reason why BIO continues to urge ICER to utilize a longer timeframe for this metric. Especially in the case of rare diseases, a therapy's long-term impact can be challenging to study given the size of the patient population. Thus, the five-year assessment window is inadequate to capture the full range of benefits, costs, and cost offsets of an innovative therapy to individual patients, the healthcare system, and society as a whole.

If ICER does not expand the time horizon over which budget impact is considered, the Institute may contribute to stifling the innovation ecosystem by systematically undervaluing therapies that have relatively high 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. However, if in spite of this, ICER insists on continuing to utilize the 5 year budget impact window, we urge the Institute to model—and report as summary metrics—budget impact at several time intervals, including 7 and 10 years to more adequately demonstrate the potential impact of cost offsets across the course of a patient's disease. An expansion of the modeling in this manner will be particularly relevant to certain types of payors, including those in integrated healthcare systems, large employers (e.g., those likely to see lower rates of turnover in their beneficiary populations), and federal healthcare programs (e.g., Medicare, Department of Defense, Veterans Affairs Administration).

[14] Eaddy, M.T., C. L. Cook, K. O'Day, S. P. Burch, and C. R. Cantrell. 2012 (January). How Patient Cost-Sharing Trends Affect Adherence and Outcomes: A Literature Review. *Pharmacy & Therapeutics* 37(1): 45-55.

B. Budget Impact Threshold

ICER proposes to continue to utilize the budget impact threshold, and proposes to update the metric based on more recent estimates of U.S Gross Domestic Product (GDP) growth. BIO continues to question the premise of the budget impact threshold and its relevance to clinical decision making. This threshold applies a one-size-fits-all standard to therapies regardless of their impact on patients' lives and the overall healthcare system, and is not meaningful in the context of clinical decision-making between patients and providers. In this way, it is anchored to the status quo of current innovation, which does not reflect society's call for better treatments and cures (e.g., evidenced by the Cancer Moonshot and Precision Medicine Initiatives).

Moreover, the budget impact threshold is based on the narrow assumption that annual spending on novel prescription drugs should not exceed GDP growth plus one percent, without a thorough analysis of the impact of this spending on U.S. GDP. In particular, ICER does not account for the potentially positive aspects of a growth in prescription drug spending that result in healthier patients and improved efficiency and effectiveness in the system. For example, healthier patients may be more productive, which positively contributes to GDP growth.[15] Similarly, there also is no consideration of the observation that rising income leads to higher expenditures on health (which could mean that patients are finally able to obtain the care they need).[16] Thus, artificially tying annual spending on new prescription drugs to GDP growth may result in unintended consequences that introduce inefficiencies into the healthcare system, not least of which through decreasing patient access to needed therapies.

C. The Value Framework's Reliance on Quality-Adjusted Life Years (QALYs)

ICER proposes that the Value Framework continue to rely on QALYs, despite BIO's and many other stakeholders' opposition to the use of this flawed metric. We raise serious concerns with the premise of imposing an average cost-per-benefit metric in a value assessment framework as it inherently obscures the benefits of increasingly personalized medicines to individual patients. This type of metric also will not be able to distinguish between the costs and cost offsets of a therapy to different stakeholders (e.g., a patient, a provider, a payor, and/or the federal government).

Specifically, BIO continues to oppose the Value Framework's use of QALYs on the following grounds:

- A QALY-dependent clinical comparative effectiveness threshold shortchanges the impact of innovative medicines on individual patients as it measures an *average* and it undermines efforts to support personalized medicine.

---

[15] Department of Health and Human Services (HHS), Office of the Assistant Secretary for Planning and Evaluation (ASPE), *The Effect of Health Care Cost Growth on the U.S. Economy*, available at: https://aspe.hhs.gov/sites/default/files/pdf/75441/report.pdf (last accessed April 1, 2017).
[16] Id. at 9-11.

- QALYs are not meaningful in the context of a multi-payer insurance system. In the U.S., in contrast to countries with a single payer system, there is no single budget against which to determine "willingness to pay" over the lifetime of the patient.
- QALYs cannot adequately capture the comprehensive value an innovative therapy offers individual patients, the healthcare system, and society.
- QALYs are arbitrary and do not holistically assess the value of a therapy to an individual patient.
- Additionally, it is unclear to what extent changes in quality of life as measured by changes in QALYs are meaningful to patients.

We urge the Institute to re-review our previous comments for a more detailed discussion of each of the concerns and the negative impact the continued use of a QALY-based value metric will have on patients and longer-term incentives for innovation.

Additionally, BIO is concerned that ICER has both proposed allowing the PACs to determine the cost-per-QALY threshold for a given Drug Review and proposed to adjust the range of the cost-per-QALY threshold downward, as low as $50,000 per QALY. With regard to the former, we are concerned with the subjective nature of the PACs determining the QALY threshold, especially given the Council members' lack of sufficient clinical expertise specific to the disease under review (discussed in more detail in section I(C)). Moreover, this approach does not provide any safeguards to ensure consistency across Drug Reviews with regard to the way in which the thresholds are set. This proposed mechanism is not evidence-based, nor scientifically rigorous, and we urge ICER to reconsider its use.

With regard to the proposal to lower the minimum cost-per-QALY threshold, to $50,000, we express strong concerns that this will further threaten patient access to prescribed medicines and undervalue innovative medicines to the extent that payers take ICER Drug Reviews into account in coverage and reimbursement determinations. This threshold arbitrarily evolved decades ago and is no longer relevant in the context of the modern healthcare system or in the context of modern biopharmaceutical innovations.[17] In fact, researchers in a 2014 New England Journal of Medicine article, who were attempting to trace the "murky origins" of this threshold, concluded that:

> All this research suggests that $50,000 per QALY is too low, although in truth it is impossible to find a single threshold to represent society's willingness to pay for QALYs gained, because different approaches yield different values, each of which is based on different assumptions, inferences, and contexts. Searching for a single benchmark is at best a

[17] In fact, research demonstrates that willingness to pay for oncology therapies may be closer to a much higher benchmark, e.g., $300,000 per QALY, than to this lower one. See Nadler E., B. Eckert, and P. J. Neumann. 2006. Do oncologists believe new cancer drugs offer good value? *Oncologist* 11(2):90-5; see also Seabury, S. A., D. P. Goldman, J. R. Maclean, J. R. Penrod, and D. N. Lakdawalla. 2012. Patients value metastatic cancer therapy more highly than is typically shown through traditional estimates. *Health Affairs* 31(4), 691-699.

> quixotic exercise because there is no threshold that is appropriate in all decision contexts.[18]

As BIO has stated in the past, we continue to be committed to value-based assessments of all healthcare technologies across sectors and stakeholders to improve the efficiency and effectiveness of the system overall. However, this does not translate to increasingly draconian cost-cutting standards that focus on perceived short-term cost offsets instead of on long-term value. The reduction of the floor of the cost-per-QALY metric on which ICER intends to rely moving forward only exacerbates the negative implications of the use of the QALY. It also ignores research that demonstrates that better health outcomes have been associated with healthcare systems that lack strict cost-effectiveness thresholds.[19] Thus, we urge ICER to reconsider this change.

D. Consistent Application of Methodological Standards

In the proposed revisions, ICER does not address BIO's concerns with a lack of robust methodological standards underlying the Value Framework, and the lapses in applying existing standards consistently within, and across, Drug Reviews. For example, BIO continues to identify a lack of objectivity when determining the comparators in draft scoping documents, which are not necessarily based on a systematic literature review of treatments in the disease area or actual utilization data on most commonly used treatments. We continue to urge ICER to address these issues by submitting the methodology for each Drug Review through a peer-reviewed process to act as an external arbiter of the validity and reliability of the assumptions made to evaluate clinical comparative effectiveness.

III. Persistent Operational Considerations: ICER should clarify critical facets of its process for operationalizing the Value Framework that remain opaque to most stakeholders.

BIO reiterates our appreciation of changes ICER has made over the course of the last several months to increase the duration of public comment periods tied to certain elements of the Drug Review process. We encourage ICER to continue to dialogue openly on this issue and reassess whether the duration should be further extended to allow a broader audience to participate. As we have noted previously in this letter, public comment periods of at least 30 days—for draft scoping documents—and at least 60 days—for more dense documents like the draft evidence review—are recognized standards for public comment periods.

Despite this progress, BIO continues to express concern that aspects of the ICER Drug Review process remain opaque to stakeholders. The process for reviews is not consistently standardized, leaving many stakeholders to devote significant resources to engaging ICER, and effectively prohibiting those stakeholders without such resources from being able to offer

---

[18] Neumann, P. J., J. T. Cohen, and M. C. Weinstein. 2014. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. *New England Journal of Medicine* 371:796-797.

[19] Kaczynski T., B. Serafin, P. Przada-Machno, and M. Kaczor. 2015. Is the cost-effectiveness threshold cost-effective in cancer therapy? *Journal of Health Policy & Outcomes Research* 2:69-78.

feedback in the first place. The following areas are key examples of the need for great clarity in how each element of the Drug Review process functions:

- The process for choosing therapeutic areas/clinical indications to study and obtaining input from clinical experts; and
- Which stakeholders ICER engages in the development of a Draft Scoping Document and how the feedback received is taken into account.

First, it remains unclear how ICER chooses which therapeutic areas will be studied. While BIO appreciated ICER's release of a list of diseases and conditions likely to undergo a review at the beginning of 2016, stakeholders have little insight into the criteria used to compile the list, what stakeholders had input into the list, and how often the list would be updated. Stakeholder input is important insofar as it could inject practical considerations into this process, including preemptively identifying methodological concerns with the study of certain therapies. One such concern, for example, is with ICER's aim to assess therapies that have not yet been approved by the FDA. These therapies often lack sufficient clinical effectiveness data to allow the therapy to be considered. Moreover, since they are not yet available on the market, they do not have a list price that can be used as the starting point for calculating net cost, and there may be little—or no—data based on which to estimate off-label use.

For example, ICER's review of obeticholic acid for treatment of nonalcoholic steatohepatitis (NASH) preceded FDA approval for this therapy, raising concerns from among those in the patient and provider community that it preceded a clinical consensus on standard of care for these patients.[20] FDA is the national regulatory authority responsible for judging clinical safety and efficacy and bases approval decisions on a robust body of evidence that has been specifically submitted to the Agency for this purpose. While in some cases, robust clinical evidence already exists at the time of FDA review of an off-label use of an approved medicine—for example, in the form of inclusion in nationally-recognized clinical guidelines documents—this is not always the case (exemplified by the obeticholic acid example). Any effort to pre-judge the appropriateness of a therapy to treat a specific clinical indication before FDA review has been completed inappropriately supplants the Agency's authority. Thus, in the future, BIO strongly urges ICER to omit any therapies that have not yet been approved by FDA—including unapproved indications of approved therapies—from a Framework evaluation until such a time as the Agency has ruled on approval. Instead, as we have previously recommended, a value assessment of an innovative therapy should be considered only once sufficient real-world evidence of use, impact, uptake, and net costs are available.

Once ICER chooses a therapy to study, it is also unclear whether the Institute seeks input from clinical experts to identify the comparative clinical effectiveness questions that are most relevant to patient care. This is a critical component of the development of an assessment of the comparative value of health interventions, which can help ensure the result is relevant to patients

[20] For example, see New England Comparative Effectiveness Public Advisory Council, 2016 (July 26), *Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-based Price Benchmarks Evidence* Report, Appendix H. Public Comments, p. 85, available at: https://icer-review.org/wp-content/uploads/2016/07/NECEPAC_OCA_PBC_Evidence_Report_FINAL.pdf (last accessed March 30, 2017).

and their providers. BIO appreciates that ICER identifies the "Expert Report Consultants" who contributed to each Draft Evidence Report, but we encourage the Institute to identify specifically: (1) when in the Drug Review development process ICER engages clinical experts to obtain input on the scope and direction of the clinical comparative effectiveness review sections of the Review; (2) what process is utilized to engage and obtain input from clinical experts; and (3) how that input is considered and incorporated, or not, into the various draft documents associated with a drug review.

Second, BIO raises concerns with the information available at the time of the public release of draft scoping documents. The draft scoping document is the first indication of how ICER intends to approach a specific topic. We appreciate that ICER has noted increased outreach to stakeholders to seek guidance in drafting this document, and that ICER has created a new "Open Input" period to inform the drafting of the scoping document. However, we urge ICER to clearly identify which groups it engages, how stakeholders can get involved in this early stage of planning if such opportunities exist outside of the "Open Input" period, and to what extent stakeholders' feedback is incorporated in the draft scoping document. BIO urges ICER to provide clarity with respect to these issues in the final updated version of the Value Framework.

Furthermore, when conducting a disease area assessment, if ICER changes the scope of its assessment or key inputs to the draft scoping document mid-review, ICER should commit to proactively notifying stakeholders of such changes and allowing them to submit comments in response to such changes. These measures are critical to ensure stakeholders are able to meaningfully participate in the full Drug Review process. As an example of an instance in which such an approach should have been applied, we note that during ICER's assessment of medicines that treat psoriasis, the Institute changed pricing inputs midway through the assessment without engaging in any dialogue with manufacturer stakeholders, resulting in erroneous net price calculations in ICER's draft evidence report. We urge ICER to correct this gap in its current process in future Drug Reviews.

IV. Conclusion

BIO appreciates the opportunity to provide comments on the underlying Framework methodology. Moving forward, ICER must establish a formal process for soliciting and incorporating stakeholder feedback on the underlying methodology in a timely fashion as the standard for value assessment evolves.

We also urge ICER to more clearly state that its work is only a single input into the broader discussion on improving the efficiency and effectiveness of healthcare decision making. The Institute also should emphasize the limitations of the drug reviews and support the importance of individual patient/provider decision making in any discussions that address payers' coverage and reimbursement determination processes. As a substantive contributor to the discussion of value, ICER has a responsibility to ensure that its process is inclusive, its methodology reflects the realities of patient care, and its findings are interpreted in the appropriate context.

BIO looks forward to opportunities to contribute to ICER's ongoing work, and continues to encourage the Institute to refine the Framework to ensure that it promotes, rather than acts at odds with, patient-focused health care. 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.

Sincerely,

/s/

Laurel L. Todd
Vice President
Healthcare Policy & Research