

Amgen Response to ICER's Draft Background and Scoping Document on Upadacitinib and Other Treatments for Rheumatoid Arthritis

SUMMARY OVERVIEW

Amgen appreciates the opportunity to comment on ICER's Draft Background and Scoping Document for the Condition Update to its 2017 Rheumatoid Arthritis Assessment. The heterogeneous presentation of moderate to severe rheumatoid arthritis (RA) means each patient experiences the burden of this disease differently and there is no typical RA patient or treatment approach. Because of this, preserving treatment choice is a cornerstone of RA therapy. Having worked in RA for several decades, Amgen as a science-based company is committed to building on this legacy by furthering treatment advances for RA patients in the areas of new medicines and biosimilars. Equally, we seek to see all products assessed according to their full holistic value to patients and society, not just the value to the payer. We appreciate that ICER continues to take steps to incorporate elements that are important to patients and reflective of real-world clinical practice. Along these lines, as part of this update, we would like to highlight a few important considerations for ICER:

- 1) **ICER has classified this as a Condition Update not a full re-assessment, and should reflect this in the methods and process, similar to ICER's psoriasis update.**
- 2) **ICER's base-case for long-term cost-effectiveness analysis in this update should reflect both the treatment value to patients and the long-term treatment benefits.**
- 3) **Consistent with prior assessments, all available biosimilars should be considered rather than using just one as an example.**
- 4) **ICER should evaluate biosimilars in the same way as the reference product and not treat biosimilar products as a separate class or category.**

A more comprehensive discussion of these recommendations is below.

KEY RECOMMENDATIONS

- 1) **ICER has classified this as a Condition Update not a full re-assessment, and should reflect this in the methods and process, similar to ICER's psoriasis update.**

As noted by ICER, this update should focus on treatments approved and new evidence available since the original ICER report in 2017; and upadacitinib, expected to be FDA approved in the coming year. The limited published evidence for upadacitinib has shown efficacy consistent with the ICER 2017 RA network meta-analysis, therefore, it would be expected that this update will further reinforce the clinical value in RA patients.¹

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2) ICER’s base-case long-term cost-effectiveness analysis in this update should reflect both the treatment value to patients and the long-term treatment benefits.

Commonly accepted methodologies in HTA include the patient perspective in the base-case to provide more meaningful results.^{2,3,4,5} We urge ICER to consider this and incorporate this perspective into the primary results of ICER’s evidence report. To better serve patients, this analysis should reflect both tangible and intangible costs that patients experience as a result of this debilitating disease, many of which are offset by the right choice of treatment at the right point in a patient’s disease, with a care protocol specifically designed to address RA’s varied and very personal manifestation.^{6,7} ICER should incorporate potential long-term treatment benefits that alleviate disability and loss of independence. In the 2017 model, HAQ scores were generated from clinical trials that do not accurately measure the potential detriment of undertreatment seen with methotrexate (MTX) alone. Given the potential long-term benefits of RA treatment, real world data on conventional disease-modifying antirheumatic drug (cDMARD) therapy would provide improved estimates of effectiveness.^{8,9} In addition to efficacy, safety has been an important consideration by patients and physicians, and ICER should closely review the profile and evidence of these treatments.^{10,11,12,13}

3) Consistent with prior assessments, all available biosimilars should be considered rather than using just one as an example.

The introduction of a biosimilar marks a significant milestone in the treatment landscape for RA. Biosimilars present the opportunity for more treatment options for patients and potential savings for the healthcare system. Hence, ICER should not treat biosimilars as individual ‘brands’ or entities but as a group of non-differentiated treatments with demonstrated similarity to reference products. In keeping with this, ICER’s update should further include *all* available biosimilars, including Renflexis® and Ixifi™ in addition to Inflectra®.¹⁴ By approaching this analysis in this way, ICER has the opportunity to help accelerate patient treatment with all biologics, not just a limited few. Equally it aligns with precedents in how ICER has considered biosimilars in prior assessments and updates.

4) ICER should evaluate biosimilars in the same way as the reference product and not treat biosimilar products as a separate class.

A biosimilar is not a new category of medicine, but an FDA-approved compound deemed highly similar to a prior approved biologic medicine. Highly similar is defined by the FDA as having no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) when compared to an existing FDA-approved reference product.¹⁵ ICER has indicated in their 2017 RA Evidence Report that, “evidence accumulated to date suggests that they [biosimilars for RA] are

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clinically equivalent to the originator products.”¹⁶ The totality of evidence, including analytical, non-clinical and clinical data is the basis of the FDA assessment of the biosimilarity of a drug and of the marketing authorization in all approved indications of the reference product, including those in which the biosimilar has not been studied in a phase three clinical study. To be consistent with this, it is important not to create the perception that these are a separate category, which implies a notable difference from the originator (in this case infliximab).

CONCLUSION

Amgen has been committed to helping patients in rheumatology for over 25 years, and is dedicated to continuing innovations to support these patients. As a patient-focused organization, Amgen is invested in continuing patient access, and we recognize that the patient perspective and impact is critical. For instance, based on patient feedback for our products, Amgen developed lower pain formulations, easy to use devices, and symptom trackers to aid in better disease management for patients. To increase the treatment options in this space, we have also used our manufacturing capabilities to develop biosimilars and have submitted a biologics license application (BLA) for our biosimilar infliximab candidate ABP 710 to the FDA, which is currently under evaluation.¹⁷ We believe it is important to consider these elements and preserve patient treatment choice for all RA treatments based on individual patient needs, specific disease characteristics, clinical expertise and patient preference. We appreciate the opportunity to comment and are hopeful this update will continue to support the need for RA patients to have treatment options and access to all needed RA therapies. In the event that the ICER team has any questions regarding how best to incorporate our recommendations into this Condition Update, please do not hesitate to contact us.

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April 30, 2019

Institute for Clinical and Economic Review
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RE: Targeted Immune Modulators (TIM) for Rheumatoid Arthritis: Effectiveness and Value; Condition Update; Draft Background and Scope

To Whom it May Concern:

The Arthritis Foundation, representing over 54 million American adults and children with arthritis, is pleased to offer comments to Institute for Clinical and Economic Review (ICER) on its draft scoping document for targeted immune modulators (TIM) for rheumatoid arthritis (RA).

Arthritis Foundation Background with ICER

The Arthritis Foundation worked with ICER on its 2017 RA review in the following ways: providing comment on the draft scoping document and draft evidence report; identifying and facilitating the involvement of a patient representative, Jan Wyatt, who attended the final meeting and provided testimony; and conducting a survey of 3,186 patients on their experiences with biologics. Key findings from that survey:

- Many respondents had tried several drugs over the course of their disease
- Many respondents had to change drugs early in their disease treatment
- Many respondents experienced significant barriers receiving doctor-prescribed medication
- The most common response to what happens when your disease is not well controlled was requiring more medications for things like pain and depression

Upon release of the final report in 2017, our comments included:

- We were pleased to see recognition of administrative burden and the need to streamline and reduce prior authorization and step therapy requirements, including allowing patients who are stable on an effective treatment to remain on therapy if their insurance changes.
- We were concerned that: the study analysis was narrow and did not include a representative sample of people with RA, and therefore was not relevant to all people with RA; the conclusions reached were based on inadequate performance measures; the reliance on QALYs was inappropriate for this disease population; and there was an absence of real-world evidence and patient experience data in the final analysis.

Real-World Use of ICER Reviews

Since publication of the 2017 RA review, we have been interested in how ICER reviews are being utilized by payers and other stakeholders. Some key examples include:

- CVS announcing in 2018 that it will consider ICER data, and in particular using the \$100,000 QALY threshold, to determine formularies
- A Premier survey showing payer use of value assessments, and in particular the evidence reports for their P&T Committee deliberations
- State Medicaid programs are beginning to adopt methodologies that rely on comparative effectiveness reviews like those from ICER to make formulary decisions; NY is one such state, and several states are also considering action

In its evidence report, we urge ICER to consider the ways in which payers are using these evidence reports and the potential implications. For example, if the CVS proposal were applied to the 2017 RA analysis conducted by ICER, it would result in significant limitations to available drugs. All targeted-immune modulators in ICER's 2017 analysis exceeded cited thresholds for cost effectiveness, and only etanercept in use with conventional DMARDs was within ICER's cost-effective willingness-to-pay threshold as a first line targeted immune modulator.

The Arthritis Foundation maintains that while the initial ICER review advanced a systematic process for comparative pharmacoeconomics, many concerns remain about the core methodologies and their applicability to chronic disease states, particularly RA.

Heterogeneity of Effects Across Populations

As the 2017 report correctly notes, there remains considerable heterogeneity of effects across the patient population. The report also acknowledges the need to "fit" treatment to patients. We remain concerned that reporting point-estimate averages on the value of treatments becomes potentially very harmful, especially if these results are then taken at face value and applied as umbrella statements on relative value across the entire population. As such we would strongly recommend that ICER address this limitation of the 2017 analysis by running scenarios for particular subgroups based on biomarker results, or other patient or disease characteristics. This would be informative to potential decision-makers in terms of understanding the variance in value across treatment strategies as well as preventing the harm that could be caused by gross oversimplification of complex sets of outcomes.

These analyses would help prevent misuse of the ICER analysis in a manner that might use a single cost-effectiveness ratio as a proxy for value for all potential patients. The real-world consequence of such misuse is reduced access to a therapy for individuals for which that therapy would provide significant value if delivered in a timely fashion.

Populations

- The scoping document includes only moderate-severe disease activity. As in our previous comments, we believe younger patients and those with early/mild RA should be included.
- It remains unclear as to how ICER will account for the frequent occurrence of comorbidities in this population. In particular osteoarthritis is frequently found comorbid to RA and may produce confounding features that are not directly treated by the TIM

- We appreciate the acknowledgement that in addition to having scant RCT evidence, the nature of chronic diseases is that the benefits accrue over decades and often represent a mixture of therapeutic agents across which patients must cycle. Our data and others presented in the 2017 framework show that most patients cycle over multiple drugs and, in the real-world, there is no clear first line therapy.

Outcomes

We appreciate the expanded list of outcomes measures to include PROMIS, other PROs, and other factors like cardiovascular events, loss of productivity and caregiver burden, health care utilization, adverse events, and pain.

Contextual Considerations

We appreciate ICER's inclusion of other potential benefits and contextual considerations in its scope. This is a critical component for producing a more accurate assessment. However, we encourage ICER to add treat-to-target (TTT) approaches that may reduce the weight placed on other outcomes. In TTT, recommendations require the physician and patient to select from various measures of disease activity and decide on a meaningful co-produced target outcome and strategy to reach that outcome. In this rubric, the identity of the measure matters less than creating a desired target within that measure. This real-world scenario will result in therapeutic strategies that differ from the drug label. This is now incentivized in the merit-based incentive payment system (MIPS), which has economic consequence outside of the present ICER model.

Simulation Model Focusing on Comparative Value

Because of the widely recognized short-comings of QALYs as applied to chronic disease and disability, we encourage ICER to balance use of QALY by other methods. Given the heterogeneous nature of QALYs, where QALYs are used ICER should control for the nature of the utility being measured in the QALY. In addition, this scoping document indicates ICER will consider a lifetime cost time horizon because of the chronic nature of disease. This is very important and we appreciate it is recognized in the draft scoping document. The Arthritis Foundation is well positioned to offer this type of data because patients themselves would be the best source of longitudinal data; health system and claims data only covers a given patient for a short time and does not capture the full range of care and costs.

Conclusion

We urge ICER to continue working with broad groups of stakeholders, including patient and provider groups, throughout this review process. Specific ways we can provide assistance include:

- Conducting an updated survey of our patient population
- Providing insights on our surveys/focus groups of patient perceptions and use of biosimilars
- Provide mixed methods data on patient prioritization of hrQOL measures
- Identifying patients to serve on the review panel

We look forward to opportunities to engage further throughout the review process.



Disease-Modifying Anti-Rheumatic Drugs for Rheumatoid Arthritis: Effectiveness and Value

April 30, 2019

Re: Draft Scoping Document for the Assessment of Treatments in Rheumatoid Arthritis

Bristol-Myers Squibb (BMS) acknowledges the importance of understanding and fully characterizing the value that innovative therapies provide to patients, and we appreciate the opportunity to respond to the ICER/CTAF call for comments on the draft scoping document for the condition update on the *Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness and Value* report. BMS is dedicated to advancing the science of immunology and to disseminating the results of our research to ensure that our work can benefit the widest range of patients.

The ICER scoping document for the evaluation of treatments for rheumatoid arthritis (RA) includes several aspects that are critical to a valid evaluation of treatments for patients with moderately to severely active disease. BMS agrees with ICER on the following points:

- ICER’s plans to seek evidence on key subpopulations and/or data stratifications of interest (page 6). BMS encourages ICER to include the set of evidence on page 6 that ICER acknowledged was suggested by stakeholders during the open input period and in the prior report (page 6).
- The separation of classes as specified by ICER (page 6). In the past abatacept has been grouped with agents with completely different mechanism of actions (MOAs). We believe the proposed separation will allow for better comparison, especially by virtue of the biomarker data we have shared in the past 2017 assessment and during the last Open Input period that occurred last month, April 2019.
- ICER plans to include additional patient-reported outcomes as well as important clinical and health care utilization measures (page 7) such as mortality, healthcare resource utilization productivity loss, etc.
- It is not clear whether fail-first insurance protocols follow established clinical guidance (page 6). Patients often cycle through various therapies before finding the appropriate treatment
- Need to measure costs and benefits from a societal perspective (page 10).

Research Methodology Considerations and Queries

As we were reviewing the draft scoping document, we had several questions that we ask ICER to clarify in the final scoping document:

- With regards to the inclusion of data from a product not yet approved by FDA, we encourage ICER to provide more clarity on how they intend to incorporate pricing into the cost-effectiveness analysis (CEA) and budget impact model (BIM) as specified on page 3. Unapproved products do not have a list price since they are not commercially available in the US.
- BMS would like to better understand the cost-assumptions for unapproved products and Inflectra® in the BIM.
- On page 3, the document specifies “*no detailed economic analyses will be performed for the biosimilars*”. To better inform stakeholder comments we encourage ICER to specify which if any economic analyses will be conducted.

- On page 7 ICER specifies “[c]omparisons of TIMs will be conducted among drugs with similar mechanisms of action (e.g., all TNF inhibitors) as well as between drugs with different mechanisms (e.g., IL-6 inhibitors vs. JAK inhibitors)”. We encourage ICER to clarify how the comparisons between the classes will be conducted.

Recommendations

In this document, we highlight opportunities to ensure validity and transparency of the scientific approaches so that the value of the individual agents for treating RA may be accurately reflected in the final ICER model and report. To achieve this goal, BMS has the following recommendations:

1. In the assumptions for building the hypothetical cohort model as noted on page 10, ICER states “[p]atients who withdraw from a TIM (due to lack of effectiveness and/or adverse events) may switch therapy up to three times. The first switch will be to an agent with a similar mechanism of action (e.g., TNF inhibitors, non-TNF biologic TIMs, JAK inhibitors); the second will be to a drug with a different mechanism of action; and the third will be to a palliative care state that involves conventional DMARD therapy. The model’s sequential treatment pattern is consistent with the ACR 2015 Guidelines for the treatment of RA.” However, on page 13 of the ACR guidelines, it states “PICO B.7. If disease activity remains moderate or high despite use of a single TNFi, use a non-TNF biologic with or without MTX over another TNFi with or without MTX (PICO B.12 and B.14).”¹
2. As mentioned above, BMS is pleased to read in your draft scoping document that you will seek evidence on key subpopulations and/or data stratifications of interest and that you acknowledged the suggestions made by stakeholders (page 6). We encourage you to consider the specific suggestions made by the stakeholders as you seek this evidence. For instance, when evaluating distinct patient groups within the model, ICER’s analyses of treatment value should stratify by biomarkers, such as by anti-CCP antibodies, as there are analyses suggesting that anti-CCP antibody seropositivity is an effect modifier.
3. In figure 1, (page 5), BMS recommends stratifying moderate to severe patients by ACPA status. Not all RA patients follow the same disease course. Both anti-CCP antibodies and RF antibodies are biomarkers of poor prognosis, which may be associated with higher disease activity²; more rapid disease progression³; increased joint damage⁴; and increased costs.^{5,6} ACPA is associated with increased risk of CV disease outcomes, including mortality,^{7,8,9} and increased interstitial lung disease (ILD) prevalence.¹⁰
4. BMS agrees with ICER’s selection of outcomes which represent a spectrum experienced by RA patients. BMS recommends the inclusion of ILD as one of the outcomes that needs to be examined (page 7).
5. Another outcome that needs to be included is that of treatment switching. Switching has significant economic consequences, especially in instances when cycling takes place within a class. BMS has data submitted to that effect during the Open Input period during the month of April 2019. Furthermore, on page 10, one of the key model inputs should include the cost of switching.
6. BMS encourages ICER to make the economic model fully transparent and available to all stakeholders for public comment.
7. ICER should include not only direct, and but also indirect costs and benefits as part of the model’s base case analysis, in order to better reflect overall societal value.
8. Real world evidence (RWE) was not considered in the 2017 report due to the challenges of integrating RWE. In addition to pharmacovigilance data, we encourage ICER to include other

RWE as it may answer gaps of information not addressed by RCTs, such as efficacy in subpopulations, and so could be used to augment the RCT-based evidence. We encourage ICER to reconsider inclusion of RWE beyond only safety.

A couple of these recommendations are explained in more detail below.

We recommend that ICER’s analyses of treatment value stratify biomarkers such as the anti-citrullinated peptide (anti-CCP) antibodies (also known as ACPA).¹ As mentioned above, we were pleased to note in your draft scoping document that you will seek evidence on key subpopulations and/or data stratifications of interest and you acknowledged suggestions made by stakeholders. Similarly to the public calls for comments during the development of the 2017 report, we continue to recommend an analysis of biomarkers such as the anti-CCP antibodies. Seropositivity of these biomarkers has been linked to a patient’s disease trajectory, such as having more severe bone erosion,^{11,12,13} increases in the number of swollen joints¹³ and premature mortality¹³; to increased costs and resource use^{14,15}; and to treatment response.^{16,17,18,19,20} The importance of this biomarker to rheumatologists is becoming clear, as the proportion of new RA patients who have received anti-CCP testing prior to an RA diagnosis has increased dramatically from less than 30% a decade ago to over 60% in recent years.²¹ In fact, the Kaiser Health System has tested over 95% of new RA patients since 2011.²² A growing body of evidence shows that distinct mechanisms underlie disease progression in ACPA-positive and ACPA-negative patients,^{23,24,25} and that genetic factors may predispose patients toward anti-CCP -positive or anti-CCP -negative RA.²⁵

As a result we believe that in a disease with so many distinct subgroups that we properly represent the true disparity of value in healthcare for the population in need, especially where strong weight of evidence suggests that risk, severity of outcomes or treatment effectiveness may be markedly affected by a pre-classified status or category of patient.

Multiple studies in the medical-ethics literature show a general preference for health resource allocation based on individual need.^{6,26} In other words, for those whose prognosis is poorer, value thresholds should be higher. This highlights the potential value to analyzing RA subpopulations, such as by biomarkers, that are associated with severity of prognosis.²⁷

We recommend that ICER include all direct and indirect costs and benefits as part of the model’s base case analysis, regardless of the patient groups evaluated. ICER’s base case model only considers cost per QALY gained, life years gained, and remissions achieved; however, this approach ignores other sources of treatment benefits. Caregivers, for instance, provide substantial amount of support to patients; any reductions in caregiver burden due to DMARD treatment should be incorporated into the base case model.²⁸ Other sources of value—such as productivity and the insurance value to non-patients—should be incorporated into the model as well. Failing to include all sources of both cost and benefits would result in inaccurate care value estimates that do not reflect RA treatment’s true value to society.

In summary, we agree with a number of the issues that ICER identified and believe that they are crucial to measuring the value of different treatments in RA. We also encourage ICER to stratify patients in the model by using biomarkers such as anti-CCP antibodies, and to include not only direct, but also indirect costs and benefits. Furthermore, we believe a budget impact analysis would not appropriately assess the long-term cost-effectiveness and value of treatments in RA. We look forward to continuing our dialogue on these and other recommendations.

¹ Anti-CCP antibodies are a surrogate marker for anti-citrullinated protein antibodies (ACPA).

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May 1, 2019

RE: Response to ICER Draft Scoping Document (Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness and Value)

Eli Lilly and Company appreciates the opportunity to respond to ICER’s draft background and scoping document titled ‘**Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness and Value**’ released on April 11, 2019. In this update of the original ICER report from 2017, the scoping document proposes that the model framework and inputs will largely stay the same, however, we would encourage ICER to reconsider this approach. We would like to provide the following feedback for your consideration:

1. Eli Lilly and Company provided extensive comments to the previous report and many of our previous concerns remain, therefore we would like to encourage ICER to include the following suggestions:

1.1. Undervalued Impact of Rebate Wall:

ICER’s model assumed a sequential treatment framework in which each Targeted Immune Modulator (TIM) is compared as first-line therapy following failure with a conventional DMARD (cDMARD). However, the model’s assumption of equal drug access was not consistent with the approach used in the model for establishing drug costs. ICER calculated “the net drug price” based on average discounts from wholesale acquisition cost (WAC) for each drug class, which are mainly driven by the preferred status of a few biologics as well as restricted access for newer therapies. Therefore, the net drug price assumption contradicts the model framework. For a new therapy to gain access equal to that of a preferred drug, the rebate discount for the new therapy must be significantly higher than the discount for the preferred therapy. This is due to a contracting practice that is unique in the autoimmune market known as the rebate wall. As a result, new branded therapies, as well as biosimilars that launch with one indication, are unable to gain preferred formulary access “even when new drugs are shown to offer better outcomes at a lower price, because the older drugs have multiple indications and billions of dollars of sales, generating rebates that are so substantial that payers would lose money by switching to more cost-effective options for a single indication.”¹ The rebate wall that exists in the RA market has established an environment where equal drug access for new branded and biosimilars does not exist. Given this, we believe that this is a fundamental flaw of the evaluation that leads to inaccurate conclusions. The evaluation should be consistent in its assumptions and should not evaluate equal drug access with an assumption of rebate discounts based on the restricted access. Instead, ICER should consider the use of WAC with a uniform rebate discount across all drugs which is consistent with the equal access assumption. This approach will result in concordance of model assumptions and inputs, as well as more accurate evaluation of the cost-effectiveness outcomes.

1.2. Unrealistic Discontinuation Assumption:

In the current scoping document, ICER has indicated that patient withdrawal from TIM will be due to lack of effectiveness and/or adverse events. The previous report made the following assumption about discontinuation: *“Patients discontinued treatment beyond the first six months only due to the occurrence of adverse events. Patients discontinued treatment due to lack of effectiveness if they received an ACR score < 20 only during the first 6 months (ACR scores >20 were considered treatment responders)”*. Therefore, the ICER model considered the rate of adverse events (AEs) as a proxy for long-term treatment discontinuation and assumed a constant rate of discontinuation. The ICER approach resulted in a very low discontinuation rate leading to unrealistically long treatment duration with inflated costs and QALYs. Instead, for accurate model evaluation, the discontinuation probability should be a function of treatment response and time on treatment² in addition to the rate of AEs. We ask ICER to change this assumption in the upcoming model update to ensure more realistic estimates of discontinuation rates as well as impacted costs and QALYs.

2. Negative Impact of Step Therapy:

ICER correctly mentions on page 6 of the scoping document that “insurance policies often require patients to follow a specific sequence of TIM therapies, yet it is unclear whether established protocols are based on the most current clinical evidence”. This insurance practice is known as “step therapy” and requires a trial of 1 or 2 preferred drug(s) prior to using other treatment options. The current model does not allow for evaluation of this practice which has been shown to be detrimental to patients’ outcomes (data on file for a pending publication of the impact of step therapy on adherence and treatment effectiveness). Therefore, we encourage ICER to evaluate the impact of step therapy (vs. open access) in a separate model. This type of evaluation is particularly important for heterogeneous diseases such as RA given the adverse clinical outcomes and associated costs that result from non-evidence based step therapy policies. For example, in a recently published policy statement, the American College of Rheumatology noted that step therapy results in forced non-medical switching, treatments gaps, and the cessation of effective therapy.^{3,4}

3. FDA Approval Limitations:

Since the original ICER report from 2017, baricitinib has been approved in US by the Food and Drug Administration (FDA) (May, 2018) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. The recommended dose of baricitinib is 2 mg once daily.⁵ Therefore, the baricitinib clinical evaluation should follow the approved label and include data from the relevant trials of 2 mg in patients with inadequate response to one or more TNF antagonist therapies. The same approach should be applied to all comparators listed on page 6 of the scoping document and comparative effectiveness should not include clinical data for treatment doses not approved by FDA. Inclusion of on-label evidence in the clinical evaluation will produce the most accurate cost-effectiveness estimates and lead to more accurate and clinically-relevant conclusions.

We appreciate your consideration of our feedback, which should support a fair and balanced assessment of RA treatments.

Sincerely,



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May 1, 2019

Institute for Clinical and Economic Review (ICER)
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Dear ICER Review Panel:

Genentech, Inc. is deeply committed to addressing the unmet medical needs of patients with rheumatoid arthritis (RA). We appreciate the opportunity to provide comments on the Draft Scoping Document for this Condition Update. RA is a chronic and complex disease requiring a personalized approach to therapy.^{1,2} Early and timely access to therapies targeting various mechanisms of action is integral in preserving patients' physical function and reducing disability.

We encourage ICER to use this Condition Update as an opportunity to increase the relevance and utility of this report through the following recommendations:

1. Include a broader set of real-world evidence than the prior report;
2. Highlight the cost per response and number needed to treat (NNT) for response analysis as key outcome measures;
3. Systematically evaluate evidence on cycling and step therapy in RA;
4. Add contextual considerations regarding early and sustained response to therapy.

1. Include a broader set of real-world evidence than the prior report.

We discourage ICER from applying a “one-size-fits-all” approach, such as requiring a minimum sample size of 1000 patients, when incorporating real-world studies across all ICER reports. The criteria for inclusion should be tailored to the clinical context of the review and the research question of interest (e.g. comparative clinical effectiveness).

In RA, disease-specific registries and administrative claims databases provide an opportunity to compare outcomes between treatments or treatment classes in a real-world setting.³⁻⁸ For example, analyses of the Consortium of Rheumatology Researchers of North America (CORRONA) registry have observed improvements in disease activity and patient-reported outcomes in patients treated with Actemra (tocilizumab) or Rituxan (rituximab) compared to other therapies.³⁻⁵

Real-world evidence plays an important role in informing patient, health care provider, and payer decisions. Ignoring the clinical context and employing narrow inclusion criteria for real-world studies will exclude high quality studies that provide meaningful evidence. Expanding the criteria to include a broader set of real-world evidence into the assessment of value will allow ICER to align with frameworks and best practices for using real-world data to support decision making.⁹⁻¹²

2. Highlight the cost per response and number needed to treat (NNT) for response analysis as key outcome measures.

The cost per response and NNT for response analysis should be incorporated into the body of the report and “Report-at-a-Glance.” In diseases where response/remission criteria are clearly defined and assessed as part of most clinical development programs, a cost per response and NNT for response analysis is an opportunity to augment the assessment of value in ways that are meaningful and interpretable for many stakeholders.

The primary treatment goal for the management of RA is to achieve low disease activity or remission.^{1,2} Attaining remission prevents the progression of joint damage, optimizes physical function, and improves health-related quality of life for patients with RA. Response to therapy is a meaningful endpoint to patients, providers, and payers. Since cost per quality-adjusted life-year (QALY) analyses report all outcomes in one aggregate measure, they may not reflect specific outcomes most important to patients (e.g. remission) in a transparent manner.¹³⁻¹⁵

Discussing responder analyses in conjunction with the cost-effectiveness results would mitigate limitations associated with cost per QALY analyses and provide a more comprehensive evaluation of a product’s value.¹⁶⁻²⁰ Expanding this discussion to include responder analyses between biologics, rather than just versus conventional disease-modifying anti-rheumatic drugs (DMARDs), could better meet the needs of stakeholders. Overall, this approach would allow ICER to align with patient and provider preferences as well as treatment goals in RA, increasing the relevance and utility of the report in health care decision making.

3. Systematically evaluate evidence on cycling and step therapy in RA.

A systematic evaluation of evidence on cycling and step therapy in RA should be incorporated into the report (“Other Aspects of Treatment”, “Other Benefits or Disadvantages”), “Report-at-a-Glance”, and policy round table discussion.

Timely access to multiple therapeutic options is crucial in the management of RA. However, inappropriate step therapy and treatment cycling can result in forced drug switching and treatment gaps.²¹ For patients with RA, these barriers can impede, interrupt, or delay access to medically appropriate care. A number of clinical and real-world studies assessing patient outcomes have supported switching to another mechanism of action after inadequate response to initial TNFi therapy.²²⁻²⁹

In response to comments on the previous preliminary report, ICER stated that the lack of a systematic evaluation of all the evidence on cycling and step therapy limited the inclusion of this topic as a voting question. By conducting a systematic review as part of this Condition Update, ICER can address this gap and have a more robust discussion on a topic that is important to payers, providers, and patients. This evaluation and discussion can better inform medically appropriate sequencing of therapies in coverage decisions and improve patient access to appropriate therapy.

4. Add contextual considerations regarding early and sustained response to therapy.

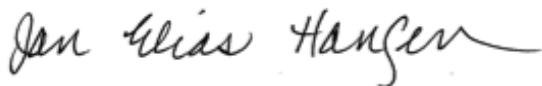
While response assessment at 6 months is the standard in clinical trials, additional considerations should be given to products that demonstrate early and sustained improvements. Treatment guidelines have emphasized the importance of achieving an early response and sustaining that target-state to prevent or delay progression of disease.^{1, 2}

In clinical studies Actemra monotherapy or in combination with DMARDs has shown rapid improvements in DAS28 and ACR response within 2 weeks of therapy with sustained improvement at 6 months.³⁰⁻³³ In patients treated with Actemra and methotrexate (MTX), response to therapy was sustained at 7 months after MTX discontinuation.³⁴ Compared to other targeted immune modulators (i.e. adalimumab), Actemra similarly demonstrated reductions in disease activity scores after 4 weeks, but at 6 months a significantly greater reduction was observed with Actemra compared to adalimumab.³⁵

Excluding additional consideration to products with evidence of early and sustained benefit may result in unnecessary barriers to timely access as patients may be required to trial or remain on therapies that may not offer a benefit.

Treatment recommendations for patients with RA require a personalized approach; however, inappropriate step therapies impede and delay access to medically appropriate care. With this Condition Update, ICER has the opportunity to address barriers to patient access and better inform coverage policies. The evidence base informing health care decisions is expanding. By adopting these recommendations, ICER can better align its framework with how stakeholders are evaluating therapies in RA, improving the relevance, utility, and impact of the report on patient care.

Sincerely,



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May 1, 2019

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Thank you for the opportunity to submit comments on the **RA Update: Draft Scoping Document**. We are pleased to note that following our conversation with the Institute for Clinical and Economic Review (ICER), several of our suggestions and input have been included in the scoping document. However, as we speak on behalf of our patient community, there remain many issues in terms of methodology and other concerns, that we, as a patient-led advocacy organization find imperative for consideration and inclusion by ICER. We continue to advocate on behalf of our patient community on the points below and would like ICER's support in this patient-centric endeavor, and hope it becomes a common objective.

We want to ensure that models recognize individual patients as an integral part of, and a valuable contributor to society. Statements on the value of individuals, and the cost-effectiveness of treatments, need to include theirs, and society's, best economic, public health, and civic interests. We believe, in the end, what is best for the patient, is in fact best for us all.

We submit the following response to ICER's RA draft scoping document.

1. Firstly, because rheumatoid arthritis (RA) is a multi-dimensional disease, it is paramount to include Patient-Reported Outcomes (PROs) as relevant endpoints along with the American College of Rheumatology (ACR) criteria, DAS-28, Health Assessment Questionnaire (HAQ) and other radiological reference documents. We believe ICER and GHLF/CreakyJoints want to capture a wholistic and more accurate picture of the therapeutic response to any intervention for a patient. In addition, RA patient populations are not homogenous in nature. They are a diverse group of individuals, and in order to reflect the diverse patient experience, evidence must be sought to include the heterogeneity of RA patients to account for this diversity. This means including populations and subpopulations of TIM naïve patients, those who have responded inadequately along with those who have responded adequately, patients with comorbidities and with different levels of disease severity (including mild) as well as patients from different races and socio-economic backgrounds. This has implications on access issues which may affect whether, and when, a patient may be able to initiate treatment and change treatment. This in turn may be explained by a coverage/insurance related reason.
2. Several issues arise with certain methodologies and measures used by ICER that we could work on together to make more patient-centric. Quality-Adjusted Life Years (QALYs), while certainly a useful academic tool, do not reflect adequately the real-world patient

experience and hence remain controversial among many experts. In addition, and related to the first point, because of each patient's unique and multi-dimensional experience with RA that includes subjective experiences related to pain or fatigue for example, the QALY may not be relevant for an RA population.

3. We welcome ICER's recognition of the limitation of including only clinical trial data. However, we note that the only reason for not restricting the model to clinical trials data alone does not have to do only with the non-inclusion of real-world data (RWD) and real-world evidence (RWE) as stated by ICER in the scoping draft. Clinical trials data also underscore why patients may discontinue treatment. This is not merely limited to adverse side effects, but may have other causes too, such as patient preference issues, non-tolerability issues that are not adverse in nature, or because the medication may not be working well enough. Again, we could work together on these, and other issues, which need to be considered and included into ICER's model. Further, clinical trials data may not entirely reflect the real-world experience where patients may not be followed as closely as when on a clinical trial and may also focus on more short-term outcomes as opposed to the longer-term experience that patients have when living with a chronic disease.
4. ICER uses a "lifetime horizon" for calculating cost-effectiveness. However, the experience of patients living with a chronic disease like RA may not be consistent over a lifetime. There are interruptions and periods of flares, remission, low disease activity. This waxing and waning remains a hallmark of living with a chronic disease like RA. Patients often report that they never know what the next day, week or month could feel or be like. Treatment may accordingly be adjusted by their clinicians. This is an integral part of the RA patient's experience and in the interest of scientific accuracy and credibility, we think must be incorporated to reflect the chronic nature of the disease.
5. ICER postulates the sequential treatment cohort model in a homogenous cohort where patients may switch therapy up to three times with the third being the adoption of a palliative care state that involves a conventional DMARD. We want to re-assert that unfortunately, this does not reflect the real-world experience of the RA patient who may need to switch therapy several times before finding a therapeutic agent that may finally work well. We welcome ICER's recognition following our conversation with them that it is not unusual for patients to try out several therapies before finding the one that may work best for them. The ICER model would be improved if it re-evaluated how to take into account a more real-world experience with additional sequences of medication change via a trial and error process by which patient and clinicians may ultimately find a therapy that works. Practicing rheumatologists can be instrumental in achieving this critical trial and error perspective and its effect on the report.
6. It is important to us, and the patients we represent, that biosimilars are portrayed as the full equivalent to biologics that science has proven them to be and that the FDA says they are. Any perceived difference by patients, physicians or insurers, could hurt their chances of success and deprive the American health care system of billions of dollars in savings. ICER has the opportunity to help ensure that biosimilars are perceived in this way and we would

like to see all applicable biosimilars included in the review if this not already the case. Such inclusiveness could extend to innovator biologics, too

We believe the focus for ICER should not remain on why certain treatments may be too expensive to be worthwhile for patients but instead on how and why treatments and drugs can be made more cost-effective so patients can benefit from them, and live better-quality lives. We also believe that this will occur as ICER begins to incorporate real world data and evidence. We, along with the clinicians, and researchers that we work with, strongly feel that integrating the patient voice, preference, and perspective, into the ICER model, especially for a disease like RA, remains paramount.

CreakyJoints, through a multi-year PCORI contract, has built and is populating a patient-reported-outcomes registry of nearly 20,000 people with arthritis. It is called ArthritisPower and collects real world data and patient reported measures that can be combined with clinical and payer data to provide a picture of the real-world experience of RA patients.

We welcome continued conversations and pathways to engage with ICER to ensure that every patient is being adequately represented before making policy level changes.

Sincerely,



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May 1, 2019

Submitted electronically to: publiccomments@icer-review.org

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

*Re: Draft Scoping Document on Targeted Immune Modulators for Rheumatoid Arthritis
(Condition Update)*

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER’s draft scoping document for its upcoming condition update on targeted immune modulators for rheumatoid arthritis.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Draft Scoping Document Comments

ICER’s “Draft Background and Scope” document, dated April 11, 2019, identifies several important considerations, including issues that emerged during ICER’s original 2017 evaluation of targeted immune modulators for rheumatoid arthritis. I urge you to take these points into consideration as ICER conducts its updated review.

First, the conclusions from the original study relied upon a homogenous patient population. As IfPA noted in its February 16, 2017 response to the initial “Rheumatoid Arthritis Draft Evidence Report,” the homogenous population creates material limitations to the findings’ general applicability. The scoping document for the updated analysis states that, in response to the feedback ICER received on the original study, ICER intends to include “key subpopulations” and “data stratifications” into the 2019 analysis. Such considerations are essential; otherwise, the updated findings will suffer from the same limitations as the original study.

Second, the scoping document notes that patient advocacy organizations have emphasized the importance of considering rheumatoid arthritis' impact on caregivers, also a concern raised in IfPA's February 16, 2017 letter. Once again, IfPA encourages ICER to include these considerations in its updated analysis.

Finally, the scoping document highlights the input from stakeholders who noted that "through the use of biologics very few patients progress to disabling joint deformities." IfPA urges ICER to make this important point more than simply a perfunctory statement. The value created by treatment success, in terms of patient outcomes, health care savings, reduced costs on caregivers, and the increased productivity of patients living with RA, all deserve consideration in the analysis.

Several concerns regarding ICER's intended methodology are evidenced in the scoping document as well.

First, the scoping document states that "we expect to integrate these new data in an updated network meta-analysis (NMA) as well as our evaluations of long-term cost-effectiveness and budgetary impact." NMAs are a complex and evolving methodology. Moreover, the well documented limitations of NMAs are particularly relevant to targeted immune modulators and warrant caution in NMAs' use for the updated analysis. NMA analyses assume, for example, that all interventions included in the "network" are equally applicable to all populations and contexts, a condition clearly inapplicable to TIMs. NMA analyses also may introduce study selection bias.

Second, the scoping document argues that "the *economic model found* that all TIMs *provide substantial clinical benefit* in comparison to conventional DMARDs alone" (emphasis added). The statement raises important concerns. Economic models do not determine a medicine's clinical benefits, and we urge ICER to ensure that its analysis does not conflate these considerations when evaluating the clinical benefits TIMs provide patients. As noted earlier in the scoping document, from a clinical perspective TIMs help ensure that "very few patients progress to disabling joint deformities."

Third, while the review will examine at least "one biosimilar, such as Inflectra®" the scoping document continues claiming that "no detailed economic analyses will be performed for the biosimilars." Excluding biosimilars from the economic analysis is a puzzling, if not seriously concerning, oversight. As less expensive versions of the originator biologics, biosimilars bring an important dynamic to the question of cost-effectiveness. Not including these products in the analysis could insert a bias toward higher cost, precipitating findings that could ultimately jeopardize patient access to these medications.

Fourth, the scoping document's plan to "develop a cohort model to assess the cost- effectiveness of each of the TIMs listed earlier relative to conventional DMARDs as well as against alternative TIM agents" is disconcerting. Not only is comparing the relatively inexpensive DMARDs to targeted immune modulators an unreasonable cost comparison, targeted immune modulators are often prescribed after patients have failed on DMARDs. Clinically, the patients who can benefit from DMARDs may differ dramatically from the patients who can benefit from targeted immune

modulators. It is not beneficial to compare the cost effectiveness of these medicines against one another.

Fifth, despite recognizing that there are other important burdens, such as the economic burden from rheumatoid arthritis on caregivers and potential productivity losses, the scoping document states that “the economic evaluation will be from a health care sector perspective, and will thus focus largely on direct medical and pharmacy costs.” Should the report focus only on the direct medical and pharmacy costs, and ignore the many other costs that are noted throughout the scoping document, the potential benefits of targeted immune modulators will be significantly undervalued.

Finally, IfPA has concerns about the inclusion of analyses that identify “lower-value services in the same clinical area that could be reduced or eliminated.” Patients, particularly rheumatoid arthritis patients, are a diverse group. Treatment options that provide high value for some patients are less efficacious for other patients. Even if the value for other services declines for some patients who benefit from targeted immune modulators, this may not be the case for other patients, or for patients who are well treated by DMARDs. Therefore, eliminating or reducing access to other services will likely have a negative impact on patient well-being.

Conclusion

IfPA urges ICER to account for these considerations so that its draft evidence report does not provide an inaccurate picture of the benefits that targeted immune modulators offer patients living with rheumatoid arthritis, particularly those whose conditions would not otherwise be well managed.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,

A handwritten signature in cursive script, appearing to read "Brian Kennedy".

Brian Kennedy
Executive Director

REMICADE, SIMPONI, SIMPONI ARIA

ICER Rheumatoid Arthritis DRAFT SCOPING DOCUMENT – Response to Request for Public Comments

The enclosed information has been supplied to you in response to your unsolicited request. Information contained in this response is not intended as an endorsement or promotion of any usage.

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EXECUTIVE SUMMARY

- The price customers pay for infliximab products, including Remicade®, is falling as illustrated in the product ASP as published by CMS (see figure below). Infusible innovator biologics and biosimilars are typically reimbursed under the medical benefit design and ASP or net price should be considered when assessing financial impact of biologic therapies.
- It is important to take into account the differences between biosimilars and interchangeable biosimilars.
- Real world switching studies evaluating innovator biologics and biosimilars provide additional perspective that is important to consider, especially for sequencing treatment within a cost effectiveness analysis.

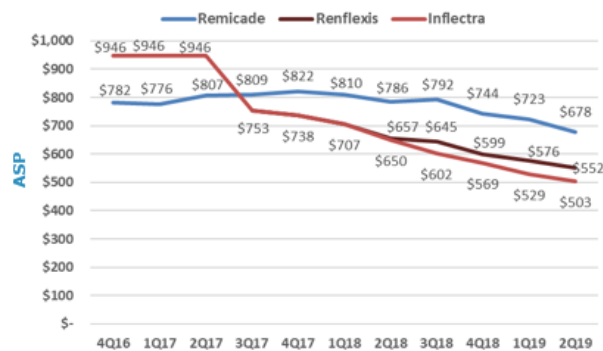
SCOPE

Pricing

- Contrary to the draft scoping document, that states “TIMs for moderate-to-severe RA are expensive, there is evidence that both their prices and the proportion of those costs paid by patients have increased substantially in recent years,” the cost of all infliximab molecules has been decreasing.

Biosimilar pricing is not always reflective of generic like pricing

- At launch, biosimilar manufacturer chose to price Inflectra so that Medicare costs were higher for biosimilar than for innovator products during the first few quarters - Inflectra cost CMS 21% more than Remicade at launch (Q42016)



List Prices:



- The prices customers pay for infliximab products, including Remicade[®], are falling as illustrated in the product average selling price (ASP) as published by CMS. Infusible innovator biologics and biosimilars are typically reimbursed under the medical benefit design and ASP or net price should be considered when assessing financial impact of biologic therapies.

Settings

ICER should include real world studies, including from ex-U.S. settings, to further evaluate differences between innovator biologics and biosimilars for a holistic representation of the impact on patients and healthcare systems.

Potential Other Benefits and Contextual Considerations

Many biologics (such as Remicade[®]) are used to treat chronic, progressive diseases requiring a lifetime of therapy. It can take years of trying multiple medications for a patient to find a therapy that is effective, and patients often prefer not to switch medications if they are stable. For patients already on therapy (any therapy, but particularly an infused immunotherapy such as infliximab) who are clinically stable, switching to an alternative treatment for reasons other than patients' health or safety (i.e. non-medical switching [NMS] for non-medical reasons) raises clinical and cost issues.

- Many prescribers prefer not to switch biologic treatments in a stable patient unless there is evidence that such a switch will have the potential to improve outcomes. Biosimilars, which, by definition, do not offer improvements in efficacy or safety, offer no clinical reason to switch.
- In a recently published study, the majority of U.S. physicians surveyed from June 2016-January 2017 preferred that their clinically stable patients not undergo non-medical switching to biosimilars and suggested that policies that compel non-medical switching in stable patients would disrupt the physician-patient relationship.¹
- In a recently published study, U.S. patients surveyed from December 2016-January 2017 reported concerns about NMS, including an unwillingness to switch to a biosimilar if their current treatment was helping treat their disease.²

The above considerations should be carefully considered by ICER through a more thorough review of the literature on this important topic.

It is important to take into account the differences between biosimilars and interchangeable biosimilars. The Biologics Price Competition and Innovation Act (BPCIA) creates two distinct regulatory pathways for biosimilars and interchangeable biosimilars. Biosimilar products are not exact replicas of the innovator product, since biologics are complex proteins and cannot be duplicated exactly. Biosimilar approval must be built on a foundational demonstration, through rigorous assessment, of analytic similarity to an innovator biologic. This assessment is followed by targeted clinical trials to show high similarity – that is, that the proposed product is neither statistically inferior nor superior to the innovator biologic and that there are no clinically meaningful differences between the biosimilar and the innovator biologic. If the biosimilar product meets the requirements in one indication, the sponsor may seek approval of the biosimilar in other indications approved for the innovator product without additional studies.

The second and more rigorous regulatory pathway is the designation of interchangeability. An interchangeable biosimilar is a biosimilar that, as permitted by state law, may be substituted for the innovator biologic, without the intervention of the healthcare provider who prescribed the innovator biologic product. In order for a product to have an interchangeable designation, the product must be biosimilar to the innovator biologic. In addition, a sponsor is required to show: 1) the product is expected to produce the same clinical result as the innovator biologic product in any given patient, and 2) the risk in terms of safety or diminished efficacy of alternating or switching between the biosimilar and innovator biologic does not exceed the risk of using the innovator biologic without such alternation or switch.³ Under the BPCIA, biosimilars are not considered to be interchangeable biosimilars

unless the sponsors conduct the required clinical studies and the FDA determines that the results meet the statutory standards for interchangeability.

These rigorous standards are focused on assuring patient safety. Since providers rely upon these standards when making prescribing decisions, it is critical for them to understand that just because a biosimilar has no clinically meaningful differences with the innovator biologic, it does not mean that providers can expect the same clinical result in any given patient or that switching back and forth with the innovator biologic product poses no greater risk than using the innovator biologic without switching, as is the case with an interchangeable product.

Controlled clinical studies have shown similarity between innovator biologics and biosimilars but may not address all the outcomes of non-medical switching of stable patients. Real world switching studies show a different perspective, specifically that there may be additional considerations besides drug cost as demonstrated by the select studies below which reported higher discontinuation rates in patients following NMS to a biosimilar.

- A meta-analysis of 62 real world studies of anti-tumor necrosis factor (TNF) treatment, reported annualized discontinuation rate was 21% among NMS patients across all therapeutic areas. Among those who discontinued, the switchback rate to the innovator biologic among all discontinuers was 62% across all therapeutic areas and 71% in rheumatology specifically. Across all nine studies with control arms, the analysis revealed a statistically significant 18% increase in discontinuations in patients who switched compared with those who did not.⁴
- In the matched 6-month post-switch analysis of German claims data in IBD patients, the risk adjusted probability of being retained on treatment was 48% greater in the innovator infliximab maintenance group than in the biosimilar infliximab switch group (RR IFX=1.48, 95% Confidence Interval [CI]: 1.19-1.85, p=0.001).⁵
- In a retrospective analysis of RA diagnosis claims from a nationwide Turkish collection database, a lower proportion of RA patients that initiated and continued innovator infliximab had discontinued treatment compared to the proportion of RA patients that initiated innovator infliximab and switched to biosimilar infliximab (33.9% vs 87%; P<0.001).⁶
- A review article including 28 studies (26 real world evidence studies and 2 randomized clinical trials) of patients switched from innovator infliximab to biosimilar infliximab reported higher discontinuation rates after switching in open-label real-world evidence studies compared with rates in double-blind randomized clinical trials.⁷
- In a prospective, randomized, double-blind trial in patients of the IBD center Munich with CD and UC, discontinuation was reported in 25.2% of patients in the biosimilar infliximab switch group and 18% in the innovator infliximab group.⁸

Two NMS cohorts with innovator etanercept-to-biosimilar etanercept switches reported higher discontinuation rates in switch patients than in patients maintained on innovator etanercept despite having implemented learnings from earlier innovator infliximab-to-biosimilar infliximab switch studies. In one cohort, the investigators' second switch experience (innovator etanercept to biosimilar etanercept) was better than the first (innovator infliximab to biosimilar infliximab), but results were still worse than their historical etanercept results despite implementing patient education measures and extra monitoring to prepare patients for the switch.⁹⁻¹²

With all real-world evidence, there is a potential for selection, channeling, and other forms of bias which may confound results. For example, data related to clinical outcomes and patient characteristics that could impact utilization patterns, including reasons for treatment continuation, discontinuation, or switch may not be available.

In addition to the select publications listed above, there is further literature on biosimilar switching, that should be carefully considered by ICER especially for sequencing treatment within a cost effectiveness analysis.

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May 1, 2019

Institute for Clinical and Economic Review
One State Street, Suite 1050
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RE: Draft Scoping Document for the Assessment of Treatments for Rheumatoid Arthritis

Dear ICER Review Team:

Merck thanks ICER for the opportunity to provide comments on the draft scoping document for the assessment for rheumatoid arthritis treatments. We share your interest in promoting fair, transparent, scientifically sound methods for value assessment. Below are our comments on the scoping document and a few requests for ICER's consideration.

- 1. Merck believes that our product, Renflexis® (infliximab-abda), is within the scope of the RA review thus requests ICER to include the product in the review.**

Renflexis, a biosimilar of Remicade, was approved by FDA for treating RA in 2017. Here is a [link to the FDA-approved label for the drug](#). According to this label and the PICOTS factors described in the draft scoping document, we deem Renflexis to be within the scope of the review.

ICER currently proposes to include another biosimilar of Remicade, Inflectra® (infliximab-dyyb), in the review as the biosimilar exemplar. We strongly believe that Renflexis should be included as well. Renflexis is a clinically equivalent alternative to the originator, Remicade.^{1,2,3} While the evidence (see the attached reference list) indicates that the clinical effectiveness and safety of Renflexis are noninferior to those of Remicade, the list price (wholesale acquisition cost, or

¹ Choe, J.-Y., N. Prodanovic, J. Niebrzydowski, I. Staykov, E. Dokoupilova, A. Baranauskaite, R. Yatsyshyn, M. Mekic, W. Porawska, H. Ciferska, K. Jedrychowicz-Rosiak, A. Zielinska, J. Choi, Y. H. Rho and J. S. Smolen. "A randomised, double-blind, phase III study comparing sb2, an infliximab biosimilar, to the infliximab reference product (remicade) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy." *Ann Rheum Dis* 2017;76:58–64.

² Smolen, J. S., Choe, J.-Y., Prodanovic, N., Niebrzydowski, J., Staykov, I., Dokoupilova, E., Baranauskaite, A., Yatsyshyn, R., Mekic, M., Porawska, W., Ciferska, H., Jedrychowicz-Rosiak, K., Zielinska, A., Choi, J., Rho, Y. H (2017a). "Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results." *Rheumatology*. 56(10): 1771–1779

³ Smolen, J. S., Choe, J. Y., Prodanovic, N., Niebrzydowski, J., Staykov, I., Dokoupilova, E., Baranauskaite, A., Yatsyshyn, R., Mekic, M., Porawska, W., Ciferska, H., Jedrychowicz-Rosiak, K., Zielinska, A., Lee, Y., Rho, Y. H (2017b). "Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study." *Ann Rheum Dis*.



WAC) of Renflexis represents a 35% discount to that of Remicade and a 20% discount to that of Inflectra.⁴

We believe that, with its unique value position, Renflexis provides ICER with another good exemplar to demonstrate the value of biosimilars as a viable solution to the affordability issues in the RA treatment field. Inclusion of Renflexis in the review is essential to present an intact picture of the biosimilar landscape, provide more complete information, and raise the awareness of all biosimilar options among patients, providers, payers, and other stakeholders.

2. Based on the same rationale, Merck also requests ICER to add us to the list of key stakeholders.

Adding Merck to the key stakeholders list would allow us to better engage with ICER for the review. We would be able to have in-depth discussion of clinical data and economic modeling. If needed, we would also be able to share unpublished data and confidential commercial information (e.g., price discounts) under ICER's confidentiality policy.

3. Merck suggests ICER includes Biosimilar—including Renflexis—in the proposed economic analysis.

In the draft scoping document, ICER proposes to conduct economic analysis on all the TIMs included in the review. We suggest ICER includes Renflexis in this analysis. As previously discussed, a main value of biosimilars to the healthcare system is to bring down the cost of biologic drugs particularly those of the originators. An economic analysis comparing the three infliximab molecules from both the healthcare system and societal perspectives will help demonstrate how biosimilars may improve the affordability and cost-effectiveness of RA management.⁵

4. Merck suggests ICER integrates biosimilar data into the overall clinical effectiveness analysis instead of separating them out.

ICER currently propose to present biosimilar data separately in clinical effectiveness analysis. However, we believe biosimilar data should be integrated into the overall clinical effectiveness analysis. Although differences in study design and intent exist between biosimilars and the originators, it may still be feasible and appropriate to conduct indirect comparisons via network meta-analysis. In general, we believe biosimilars (e.g., Renflexis, Inflectra) should be treated equally to the originators (e.g., Remicade) in clinical effectiveness

⁴ <https://investors.merck.com/news/press-release-details/2017/Merck-Announces-US-Launch-of-RENFLIXIS-infliximab-abda-a-Biosimilar-of-Remicade-for-All-Eligible-Indications/default.aspx>

⁵ László Gulácsi, Valentin Brodsky, Petra Baji, HoUng Kim, Su YeonKim, Yu Young Cho & Márta Péntek (2015) Biosimilars for the management of rheumatoidarthritis: economic considerations, Expert Review of Clinical Immunology, 11:sup1, 43-52, DOI:10.1586/1744666X.2015.1090313



analyses, because these drugs share the same mechanism of action (MOA) and passed rigorous regulatory bio-equivalence approval process.

Again, we appreciate the opportunity to provide input on the scoping document for the ICER review update. We look forward to engaging with ICER as this review moves forward.

Sincerely,

A handwritten signature in black ink that reads "Fang Sun".

Fang Sun, M.D., Ph.D.
Director, Medical Policy, HTA & Value Assessment
The Center for Observational and Real-World Evidence (CORE)
Merck & Company, Inc.



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May 1, 2018

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

Submitted via email: publiccomments@icer-review.org

RE: Draft scoping document for rheumatoid arthritis condition update

Dear Dr. Pearson,

On behalf of Pfizer Inc, I am writing in response to the Institute for Clinical and Economic Review's (ICER) open input period for its rheumatoid arthritis (RA) condition update.

We appreciate ICER's efforts to seek input from a broad range of stakeholders. Life sciences companies like Pfizer devote significant resources to research, and our scientists have deep expertise in understanding the clinical, economic, and quality of life impacts of conditions like RA.

Based on our review of draft scoping document, we offer the following feedback.

ICER's methodological approach seems unchanged from 2017; our significant concerns about ICER's methodology remain unaddressed.

Previously, in 2017, Pfizer highlighted seven key concerns with respect to ICER's approach to evaluating the clinical and economic value of RA therapies.¹ Based on our reading of the draft scoping document, we believe that the same concerns will limit the validity of the outputs of the 2019 condition update.

We urge ICER to carefully re-consider its approach, and to address the following concerns with respect to the condition update.

- **Concern #1:** ICER has not addressed or adjusted its methodology to account for significant changes in RA treatments (including new mechanisms of action and new formulations), changes in regulatory guidance for clinical trial design (related to placebo controls), and the

¹ Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value. Public Comments on Draft Report March 10, 2017. Available at: https://icer-review.org/wp-content/uploads/2016/08/NECEPAC_RA_Public_Comments_031017.pdf. Accessed April 28, 2019.

impacts these shifts have had on subject enrollment demographics over time. This may result in bias against therapies that have been FDA approved in recent years.

- Concern #2: ICER's approach to treatment discontinuation and treatment switching does not reflect current standard practice. This limits the utility of results to patients, their physicians, and payers seeking to understand real-world use.
- Concern #3: ICER's approach to ACR classification has not been validated and does not reflect routine clinical practice. This limits the utility of results to patients, clinical stakeholders, and payers seeking to understand real-world use.
- Concern #4: ICER's approach to analyzing Sharp scores ignores several critical methodological challenges. This significantly limits both the validity of its findings and relevance to clinical practice.
- Concern #5: Estimation of HAQ scores is unnecessary and incongruous, given consistent measurement in clinical trials. This methodology ignores existing data, and further limits the utility of results to patients, clinical stakeholders, and payers seeking to understand real-world use.
- Concern #6: ICER's estimation of net price discounts at a class level is imprecise and does not reflect true competitive market dynamics. As a result, ICER's economic findings could be misleading and of limited use to payer stakeholders.
- Concern #7: There is no evidence that ICER's approach to stakeholder engagement, especially with respect to patients, has materially informed the report's methodology. This presents a clear challenge to stakeholders who are seeking to develop a patient-centric perspective on RA therapies.

A more detailed explanation of these concerns can be found in the public comment letter sent by Pfizer regarding the 2017 ICER draft evidence report.¹

ICER should incorporate real-world evidence into its review.

Randomized clinical trials (RCT) are considered the gold standard of clinical evidence. However, there is growing recognition that real world evidence (RWE) can and should play an important role in understanding the complete value of treatments.²

There are three key reasons why we believe it is critical for ICER to incorporate RWE in its review of RA treatments.

First, RWE may offer different / additional perspectives on clinical value when compared to RCT data. Biologic DMARDs (bDMARDs) are an important advance in the treatment paradigm, allowing some patients to achieve disease activity targets through treatment escalation following inadequate response to conventional DMARDs (csDMARDs). However, despite the availability of various

² Berger M, Lipset C, Gutteridge A et al. Optimizing the leveraging of real-world data to improve the development and use of medicines. Value Health 2015; 18(1):127-30.

bDMARDs, many patients with an inadequate response to first line csDMARDs do not initiate bDMARD agents.³ For those who do, substantial proportions fail to achieve (primary inadequate response) or maintain (secondary inadequate response) treatment targets, while others develop treatment-limiting intolerance. Measures of primary response indicate that while 25-40% of patients may achieve clinical remission at any given visit (DAS28<2.6)^{4,5,6}, approximately 50-55% achieve a state of low disease activity (LDA) (DAS28<3.2)⁴, and only 17-20% sustain remission for longer than 90 days⁷. This burden of intolerance and secondary non-response is also evident in registry data. A systematic review showed that approximately 20-30% of RA patients receiving TNF inhibitors had drug survival rates of 1 year or less.⁸ Loss of efficacy and adverse event rates were the main contributors to discontinuation. The observed differences in response rates between RCT and RWE sources suggest that any analysis based on RCT data alone is likely to reflect a biased estimate of clinical value.

Second, RWE on treatment cycling are critical to value assessment. There is evidence to suggest that a decreased clinical response occurs when patients are cycling from one TNF inhibitor to a second TNF inhibitor. In a systematic review, Rendas-Baum found that the likelihood of response to subsequent treatment with bDMARDs declined with the increasing number of previous treatments with TNF inhibitors.⁹ In addition, an analysis of 2,242 patients with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry demonstrated that the response and remission outcomes were consistently inferior for patients who switched TNF inhibitor therapies versus TNF inhibitor naive patients.⁹ Given the findings highlighted above, treatment cycling will be an important factor for ICER to consider in its assessment of comparative clinical efficacy.

Third, RWE can provide greater insight regarding effectiveness and value of combination therapy compared to monotherapy. Guidelines from the American College of Rheumatology recommend concomitant use of csDMARDs to optimize the efficacy of bDMARDs (including TNF- α inhibitors) and to reduce the immunogenicity of biologics.¹⁰ Despite some bDMARDs being approved as monotherapy, they seem to achieve enhanced efficacy in combination with csDMARDs.^{11,12,14} Despite recommendations for the use of bDMARDs with methotrexate, analyses indicate that 44%

³ Taylor PC, Alten R, Gomez-Reino JJ, et al. Comparison of biologic DMARD RA treatment dynamics across five EU countries. British Society of Rheumatology, 2016, In press.

⁴ Gabay C, Riek M, Scherer A, et al. Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. *Rheumatology (Oxford)*. 2015;54(9):1664-72.

⁵ de Punder YM, Franssen J, Kievit W, et al. The prevalence of clinical remission in RA patients treated with anti-TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Rheumatology (Oxford)*. 2012;51(9):1610-7.

⁶ Rendas-Baum R, Wallenstein GV, Koncz T, et al. Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor- α inhibitors. *Arthritis Res Ther*. 2011;16;13(1):R25.

⁷ Mierau M, Schoels M, Gonda G, et al. Assessing remission in clinical practice. *Rheumatology (Oxford)*. 2007 Jun;46(6):975-9.

⁸ Arora A, Mahajan A, Spurdin D, et al. Long-term drug survival of TNF inhibitor therapy in RA patients: a systematic review of European national drug registers. *International J of Rheum*. 2013; 2013:1-9.

⁹ Greenberg JD, Reed G, Decktor D, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Ann. Rheum. Dis*. 2012;71(7):1134-1142.

¹⁰ Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann Rheum Dis* 2012 Nov;71(11):1914-5.

¹¹ Emery P. Why is there persistent disease despite biologic therapy? Importance of early intervention. *Arthritis Research & Therapy*. 2014;16:115.

¹² Hyrich KL, Symmons DP, Watson KD, et al. British Society for Rheumatology Biologics Register. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006 Jun;54(6):1786-94.

of patients-initiated TNF- α inhibitor treatment without concomitant csDMARDs.¹³ Effectiveness analyses from data generated in routine clinical practice settings are consistent with those from RCTs, suggesting that the use of biologic monotherapy may result in lower rates of remission when compared to combination therapy.^{12,14}

We believe that RWE studies can add significant value to the ICER review and can inform ICER's perspective on several key issues in RA treatment, including treatment cycling and monotherapy use. We strongly recommend that ICER conduct a thorough literature review including different types of clinical and RWE studies for RA treatment.

We note that, as reflected in the draft scoping document, similar feedback on the use of RWE has already been received by ICER from the stakeholders it has engaged to date. We look forward to understanding how ICER will seek to address the feedback and take steps to accomplish this important goal.

ICER should reexamine its approach to reviewing biosimilars in the RA update.

In the draft scoping document, ICER notes that it intends to include one biosimilar (Inflectra) in the condition update. ICER does not explain why it has selectively chosen this particular biosimilar for inclusion, nor does ICER offer any rationale for excluding other FDA-approved biosimilars from its analysis.

ICER also states that it intends to only examine the clinical evidence for biosimilars, and that “no detailed economic analysis will be performed for the biosimilars”. This proposed approach seems counterintuitive given (a) the regulatory approval process for biosimilars, and (b) the potentially significant economic value that these treatments may bring.

With respect to regulatory approval and clinical data, the U.S. Food and Drug Administration (FDA) has stated that “a biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from, an existing FDA-approved reference product.”¹⁵ Based on the standards outlined by the FDA, it is likely that the evidence base for biosimilar products will be very different from bio-original products, which would significantly hamper pooling and comparison of data for the two different types of products.

Given that approved biosimilars have met the FDA's definition above, it seems that ICER is missing a critical opportunity in choosing to forego economic analyses of these products. A key element of the value proposition of biosimilars is the expectation that they will be priced at a discount to their bio-original counterparts. Additionally, biosimilar entry theoretically increases marketplace competition, which should impact pricing of bio-original products. Part of ICER's mandate is to articulate “the economic value each treatment represents”.¹⁶ This would suggest that the opportunity to understand how biosimilars might impact the economics of RA treatments, both in

¹³ Harnett J, Wiederkehr D, Gerber R, et al. Real-world evaluation of TNF-inhibitor utilization in rheumatoid arthritis. *J Med Econ.* 2016; 19 (2): 101-112.

¹⁴ Reed GW, Gerber RA, Shan Y, et al. Comparative effectiveness of TNFi and tofacitinib monotherapy in clinical practice: Results from CORRONA registry. *Ann Rheum Dis* 2016;75(Suppl2):228.

¹⁵ U.S. Food and Drug Administration. Biosimilar Development, Review, and Approval. Available at: <https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval>. Accessed April 30, 2019.

¹⁶ Institute for Clinical and Economic Review. About. Available at: <https://icer-review.org/about/>. Accessed April 30, 2019.

terms of short- and long-term cost savings would be within ICER's remit. Yet ICER has specifically indicated that economic value is out of scope for this review. We would suggest that stakeholders reading the RA condition update will likely be interested in biosimilar value; therefore, we ask that ICER provide further detail on why it has made the decision to forego economic analyses for this set of products.

Concluding remarks

We hope that these comments are useful to ICER as the organization continues to shape its review of RA therapies. We would welcome an opportunity to discuss the scope and methodology of the planned review with you in more detail.

Kind regards,

A handwritten signature in black ink, appearing to read 'PS', with a stylized flourish at the end.

**Prasun Subedi, PhD
Senior Director
Patient and Health Impact**

Sandoz, A Novartis Division

Submitted VIA ELECTRONIC SUBMISSION at publiccomments@icer-review.org

May 1, 2019

Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

RE: Draft Scoping Document

Dear Sir or Madam,

Sandoz, A Novartis division, is submitting this letter to the Institute for Clinical and Economic Review (ICER) in response to the Draft Scoping Document, outlining the planned review of the comparative effectiveness and value of treatments for rheumatoid arthritis (RA) that was released on April 11, 2019.¹

We hear a lot about the problem of skyrocketing healthcare costs, but few are doing something about it. We believe that biosimilars are one solution to address healthcare costs and give more patients suffering from rheumatoid arthritis access to safe and effective disease modifying medications.

Biosimilars can help provide millions of patients more affordable and accessible treatments. They create the potential to save the US healthcare system \$54 billion over 10 years.² The cost of biologics reached \$120 billion in 2017, but if all approved biosimilars had been marketed in a timely manner, Americans could have saved \$4.5 billion.^{3,4} An estimated 1.2 million US patients could gain access by 2025 as the result of biosimilar availability – with an added benefit to female, lower income and elderly individuals.⁵

Stakeholders can trust that biosimilars have the same efficacy and safety profile for patients as their reference biologics. They are FDA-approved medicines that went through a rigorous

¹ ICER RA Update: Draft Scoping Document. https://icer-review.org/material/ra-update-draft-scoping-document/?utm_source=RA_draft_scope&utm_campaign=RA_draft_scope&utm_medium=email

² Mulcahy AW, Hlaváka JP, Case SR. Biosimilar cost savings in the United States: initial experience and future potential. Santa Monica, CA: Rand Corporation, 2017. <https://www.rand.org/pubs/perspectives/PE264.html>.

³ IQVIA Institute for Human Data Science. Medicine use and spending in the US: a review of 2017 and outlook to 2022. <https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022>.

⁴ U.S. Food and Drug Administration. Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilar Action Plan [press release]. July 18, 2018.

⁵ The Biosimilars Council. Biosimilars in the United States: providing more patients greater access to lifesaving medicine. <http://biosimilarscouncil.org/wp-content/uploads/2017/09/Biosimilars-Council-Patient-Access-Study-090917.pdf>.

development and testing process.^{6,7} In a systematic literature review of 90 studies of 7 biosimilars covering 14 disease states and 14,225 patients, no new safety or efficacy concerns were detected.⁸

Sandoz is the first to bring biosimilars to US patients and the only US success story.⁹ We have proven biosimilars create early and expanded patient access to life-changing biologics – while increasing healthcare savings and fueling innovation. We have 35+ years of biologic development, 20 years of biosimilar development and 10+ years of biosimilar commercialization and patient experience.^{10,11}

Report Aim:

We appreciate the opportunity to provide comments on the Draft Scoping Document. First, we would like to share feedback on the Report Aim, specifically on ICER “will also review the clinical evidence of at least one biosimilar, such as Inflectra®; no detailed economic analysis will be performed for biosimilars.”

When ICER evaluates the clinical evidence of biosimilars it must be taken in context with the totality of the evidence. A recent review by Coory and Thorton that applied the GRADE evidence criteria to biosimilar trastuzumab found that the totality of the evidence would be categorized as high quality evidence. However, if the randomized trials were evaluated in isolation from the other studies, it could be mistakenly rated as medium-to-low quality. ICER should utilize the same approach as these authors when evaluating the evidence from biosimilars.¹²

We strongly recommend that biosimilar(s) be included in the detailed economic analysis, along with the other interventions, because the primary value of biosimilars rests in providing increased savings and access to biologic treatments. Biosimilars have the same efficacy and safety as their reference biologic but they differ in cost. Therefore, the inputs for the biosimilar for an economic analysis would be the publicly available cost data and the efficacy and safety data of the reference product.

⁶ US Food and Drug Administration. Biologic product definitions.

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf>. Accessed December 14, 2018.

⁷ US Department of Health and Human Services. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. April 2015. <https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf>. Accessed Dec 14, 2018.

⁸ Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. *Drugs*. 2018; 78(4):463-478.

⁹ US Food and Drug Administration. FDA approves first biosimilar product Zarxio [press release]; March 6, 2015. <https://wayback.archiveit.org/7993/20171105050630/https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>. Accessed 7, 2018.

¹⁰ Rios, M. A decade of microbial fermentation. <http://www.bioprocessintl.com/upstream-processing/fermentation/a-decade-of-microbial-fermentation-331179>. Published June 1, 2012. Accessed October 30, 2018.

¹¹ US Food & Drug Administration. FDA Oncologic Drugs Advisory Committee Meeting. Zarxio® (filgrastim). January 7, 2015. <https://wayback.archive-it.org/7993/20170405222933/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428782.pdf>. Accessed August 3, 2018.

¹² Coory M and Thorton K. Randomised clinical endpoint studies for trastuzumab biosimilars: a systematic review. *Breast Cancer Res Treat*. 2019 Apr 12

Additionally, we recommend that the biosimilar evidence paradigm be included in ICER's Value Assessment Framework in order to help assess the clinical and economic value of interventions.

Scope of the Assessment:

Second, we would like to share feedback on the Scope of the Assessment. When updating the prior 2017 systematic literature review on therapies, specifically biosimilar(s), for RA, ICER must consider the evidence paradigm for biosimilars when evaluating the quality of the evidence.¹³

Interventions:

Third, we applaud ICER for including a biosimilar in the comprehensive list of targeted immune modulators with FDA indications for RA.

With regards to “biosimilar data will be presented separately given differences in study design and intent relative to clinical studies of the originator products” we once again recommend that ICER consider the evidence paradigm for biosimilars when evaluating the quality of the evidence.

In closing, biosimilars can enable more patients to access biologic medicines and may offer significant savings for patients, helping to alleviate the overburdened healthcare system.^{14,15} Sandoz has the only proven biosimilar success-story of expanded patient access and cost-savings in the US and will continue to deliver on the promise of biosimilars.

Stakeholders supporting biosimilars will be part of the solution in offering patients high quality care at a more affordable price, creating a more sustainable system for patients now and for the future.¹⁶

We want to reiterate our appreciation to ICER for the opportunity to provide comments on the Draft Scoping Document. If any questions should arise about our comments, please feel free to contact us.

Sincerely,

Sanjeev Balu PhD
Director, Health Economics &
Outcomes Research
Sandoz

Kellie Calderon MD
Executive Director, Head of Immunology
Medical Affairs
Sandoz

¹³ ICER Rheumatoid Arthritis: Final Report. <https://icer-review.org/material/ra-final-report/>

¹⁴ IQVIA Institute for Human Data Science. Medicine use and spending in the US: a review of 2017 and outlook to 2022. <https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022>.

¹⁵ U.S. Food and Drug Administration. Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilar Action Plan [press release]. July 18, 2018.

¹⁶ McBride A, Campbell K, Bikkina M, MacDonald K, Abraham I, Balu S. Cost-efficiency analyses for the US of biosimilar filgrastim-sndz, reference filgrastim, pegfilgrastim, and pegfilgrastim with on-body injector in the prophylaxis of chemotherapy-induced (febrile) neutropenia. *J Med Econ.* 2017;20(10):1083-1093.