ADVERA HEALTH ANALYTICS
3663 N. Laughlin Road, Suite 102, Santa Rosa, CA 95403

September 22, 2015

Institute for Clinical and Economic Effectiveness
New England Comparative Effectiveness Public Advisory Council
One State Street, Suite 1050, 10th Floor
Boston, MA 02109

RE: Draft report titled *"PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value Based Price Benchmarks"*

Dear Sirs:

Thank you for the opportunity to provide these comments on your draft report *"PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value Based Price Benchmarks"*. We commend ICER for the hard work and careful thinking that went into the drafting.

Our comments focus on the importance for ICER to actively use federal data on post-approval adverse drug events to significantly improve the evidence based assessment of new medications against currently marketed standards of care. These drug safety data are available through the FDA Adverse Event Reporting System (FAERS). With more than 1.5 million post-approval adverse drug reactions reported annually to FAERS these data offer invaluable information regarding the real world safety of FDA approved drugs.

Coupled with advanced analytics, rigorous algorithms, and data from the Agency for Healthcare Research and Quality (AHRQ) on the direct medical costs (e.g., hospitalizations) from adverse drug events, ICER now have access to far more robust, timely, and evidence-based data regarding the true safety impact and downstream costs of FDA approved drugs. The opportunity to save lives, improve outcomes, and reduce unnecessary costs is considerable, and is now well within reach.

Unfortunately, ICER did not include an analysis of these data in the draft report, thus few health plans and no state currently uses this information when creating preferred drug lists, writing prior authorization criteria, negotiating supplemental rebates, educating prescribers and dispensers, or performing prospective, concurrent, or retrospective drug utilization review.

Absent use of, and access to this information, states and health plans spend more money on poorer outcomes, placing beneficiaries at unnecessary risk from suboptimal, costly care and even death and severe disability.

Active use by managed care programs of federal data on post-approval adverse drug events, facilitated by inclusion of these data in ICER reports will:

1. Improve outcomes for patients by helping ensure beneficiaries receive the safest medication therapy and that both prescribers and dispensers are empowered with the latest information;

2. Identify covered low-risk medications that can be substituted for high-risk drugs in order to reduce beneficiary death and disability;

3. Reduce federal and state costs by preventing hospital admissions, readmissions, and emergency department visits;

4. Improve management of drug benefits, including medical management and drug utilization review functions;

5. Ensure preferred drug lists are developed and updated using all available information including real world data on safety and the medical costs of post-approval adverse events, rather than merely emphasizing net unit costs; and

6. Support ICER expectations for comprehensive, evidence-based quality monitoring, improvement, and reporting.

Below, we describe our recommended changes to strengthen the Medicaid drug benefit within managed care programs. Following these recommendations, we provide detailed background information on the use of FAERS data and analytical tools to improve outcomes and reduce costs. To underscore the vital importance of using this information in ICER analyses, upon request by ICER we will provide data on adverse events and costs for comparator statin therapies.

Comparative Clinical Effectiveness

Meta-analyses of select adverse events data for evolocumab and alirocumab in clinical trials should not only be compared to control group, but to real world data reported to FAERS.

Disproportionally reported adverse events for comparators should be identified and discussed.

Ongoing post-approval monitoring of adverse events for newly approved medications should be conducted and included in future reports on the topic.

Comparative Value

As noted in the summary and comment section of Comparative Value, ICER did not model drug-related adverse events. Even if deemed insignificant based on available data, the cost of adverse events should be included for analysis. For comparator therapies, the cost of adverse events, calculated using post-marketing data should be included and discussed. To make an accurate budget impact decision, these costs must be considered.

Ongoing post-approval monitoring of the costs of adverse events for newly approved medications should be conducted and included in future reports on the topic

Background of Adverse Drug Events and Importance for Healthcare Decision Makers

Failing to review and react to the best possible data regarding post-approval adverse drug events puts patients at undue risk and causes significant avoidable medical costs. In 2013, the cost from reported post-approval adverse drug events was approximately $4.7 billion. Some experts believe that up to 90 percent of adverse drug events may go unreported, meaning the true cost to the healthcare system may be as much as $25 billion per year.

This has a significant negative impact on patients. In 2013, more than 800,000 serious adverse drug events were reported to FDA, resulting in more than **148,000 reported hospital admissions**, **more than 65,000 reported deaths**, and **more than 14,000 reported disabilities**. An in-depth review of all available post-approval drug safety data can make providers aware of new, serious risks of any medications provided to patients as soon as information on that new risk becomes available.

Conclusion

We strongly believe that analysis of post-approval adverse drug event data can improve patient outcomes and lower healthcare costs. Understanding the true impact of a drug must go beyond price and efficacy. Data and healthcare technologies are currently available to enable the review and analysis of:

- serious post-approval adverse events emerging from real world reporting that have not previously identified or listed on the drug's label;
- comparative rate of reported serious outcomes (e.g., hospital admissions, deaths, disabilities) among major drug classes and indications; and
- comparative costs associated with these serious adverse events and outcomes.

Thank you for the opportunity to comment on this important draft report. If ICER staff have any questions or wish further information, please contact me at brian@adverahealth.com or (707) 387-9230 x500.

Sincerely,

Brian M. Overstreet
President

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September 21, 2015

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review (ICER)
One State Street, Suite 1050
Boston, MA 02109

Submitted electronically via info@icer-review.org

RE: *PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks - Draft Report - September 8, 2015*

Dear Dr Pearson,

Thank you for the opportunity to provide comments regarding the Institute for Clinical and Economic Review's (ICER) draft report released on September 8, 2015 entitled, "*PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks*". America's Health Insurance Plans (AHIP) is the national association for the health insurance industry. Our members provide coverage to more than 200 million Americans, offering a broad range of health insurance products in the commercial market and demonstrating a strong commitment to participation in public programs.

AHIP and our members are committed to providing consumers with access to safe and effective medical treatments and preventive services. Health plans have developed a number of strategies in response to sustained cost increases that ensure access to critically important treatments and services while also holding down costs. These approaches include providing patients with tools and support to help them successfully manage their conditions and promoting team-based, collaborative care arrangements.

ICER's efforts to evaluate the comparative effectiveness and value of new and existing tests and treatments offer a common framework for payers, patients, providers and manufacturers. Unsustainable costs and the introduction of new treatments and therapies without the support of strong evidence make value frameworks like that of ICER's critically important to promoting affordability and value.

ICER's report on PCSK9 inhibitors sheds much needed light on the relationship, or lack thereof, between value and price. This report provides further justification for the need for greater transparency in drug pricing. Evidence-based justification of pricing for new medications is essential to determine the value of these products for treating or preventing disease. Reports

such as this help to uncover an appropriate price based on the improvements realized for patients. In the case of cholesterol treatments, the significance of this report is even greater as recently updated guidelines for treatment may expand the number of people who may be considered for this therapy.

Thank you again for the opportunity to provide input on ICER's draft report. AHIP and our members commend ICER's efforts in producing this report and in helping to answer the important questions regarding value and pricing for drugs. We look forward to providing input on the continuing work to promote transparency in the pricing of new healthcare treatments.

Sincerely,

Carmella Bocchino
Executive Vice President

AfPA
Alliance for Patient Access

September 22, 2015

Submitted Electronically to *info@icer-review.org*

Re: ICER's "PCSK9 Inhibitors for Treatment of High Cholesterol"

Dear Sir or Madam:

The Alliance for Patient Access (AfPA) is a national network of nearly 700 physicians working to ensure patient access to approved therapies and appropriate clinical care. Since its inception, AfPA has made comment on numerous policy matters that impact patient access including legislation, regulations, and health plan coverage limitations. On behalf of AfPA's physician members, I am writing to express concern regarding the Institute for Clinical and Economic Review's recent draft report, "PCSK9 Inhibitors for Treatment of High Cholesterol."

For patients, the immense value of a life-changing medication can be difficult to quantify. Yet AfPA members understand that, as drug prices rise, more health insurers and policymakers are working to define value based upon medical therapies' clinical effectiveness. But when market prices doesn't conform to value assessments, effectiveness data can be used to justify limiting patients' access to breakthrough treatments. As an organization dedicated to patient access and the primacy of the physician-patient relationship, AfPA finds such limitations troubling.

As ICER's report notes, newly approved PCSK9 inhibitors alirocumab and evolocumab can reduce LDL cholesterol by 55-60 percent—welcome news for millions of Americans. The study suggests that expected patient improvements correspond to a price that's 67 percent less than the therapies' listed market price. But because a significant portion of American patients need cholesterol-lowering medication, the study suggests reducing the therapies' price still further to roughly one seventh of the list price.

Physicians and patient advocates have concerns, however, about the effect that these value assessments may have on patient access. As ICER's founder explained, if the cost of new LDL cholesterol-lowering medications proves to be higher than the benchmark created by ICER, "doctors, insurers, and other parties may need to work together to determine ways to limit the use of these drugs." When data points intended to minimize health care costs are instead used to deny coverage for patients, patients miss out on approved therapies that could otherwise improve and even extend their lives.

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Analytics for assessing medications' values can also overlook the cornerstone of quality health care—the physician-patient relationship. Statistics by nature generalize patients into types instead of individuals, considering measures such as net health benefit and long-term cost instead of value for an individual patient's course of treatment. Should insurers lean too heavily on value assessments in determining coverage policies, physicians may find their ability to guide patient care very limited.

As the Comparative Effectiveness Public Advisory Council considers feedback on its draft report, the physicians of AfPA urge council members to consider the needs of patients and the importance health care in which physician insight, not analytical data points, determines which patients access which approved medical therapies.

Sincerely,

Brian Kennedy
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Dear Dr. Pearson:

Amgen is a science-based company committed to developing and delivering innovative medicines that make a difference in patients' lives. We welcome the opportunity to provide comments in response to the CEPAC/ICER request for public comments on the PCSK9 inhibitor (PSCK9i) report.

Executive Summary and Background

PCSK9i's are a significant advance in an area of enormous unmet need in lowering LDL-C, a major risk factor for cardiovascular disease (CVD). CVD remains the number one cause of premature mortality and morbidity worldwide, and causes one out of every three deaths in the United States. A fatal CV event shortens a person's life by an average of 17 years.[1,2] The annual direct and indirect cost of CVD in the US is expected to grow to approximately $600 billion in 2015.[3] PCSK9i's offer unprecedented ability to lower LDL-C and studies to determine PCSK9i's effect on CV morbidity and mortality are ongoing.

Amgen supports having a robust and balanced dialogue about the value of PCSK9i's. Such a dialogue should be based on realistic assessments of these new medicines, using well-tested and transparent methodology. Value-based discussions should keep the interests of patients at the center of the analysis. In doing so, these assessments should take a broad societal perspective related to the costs and benefits of healthcare interventions. Amgen disagrees with the methodology, conclusions, and lack of transparency of the ICER report, and does not believe that voting on questions is appropriate before these deficiencies are addressed.

Specifically, Amgen believes that ICER's assumptions and methodology have the following significant errors and deficiencies:

1. The ICER report for PCSK9i's performs a cost-effectiveness evaluation that models extensive product uptake by a population at lower risk than the FDA label and real-world adoption would suggest. An appropriately calibrated model could confirm PCSK9i cost-effectiveness within ACC/AHA thresholds for value.
2. ICER uses assumptions to assess budget impact (mislabeled as "health system value") that are not based on evidence, and which overstate the population size likely to receive PCSK9i's. For perspective, ICER estimates that PCSK9i use alone will grow to over one third of the entire US expenditure on all medications.
3. The newly proposed ICER method confuses the concept of "value" with an indiscriminant form of budget-based rationing. In defining a budget-based benchmark price, ICER has redefined value by capping price and spending on aggregated and individual medicines and limiting their growth. ICER's budget-based price benchmark is based on short-term costs (a maximum of five years) and does not include important long-term aspects of value such as assumptions around improving patient survival and avoidance of event-related deterioration in quality of life.

In summary, the ICER report underestimates CV risk in cost-effectiveness and budget impact models, overestimates the population size likely to receive PCSK9i's, overestimates drug uptake, and invents a new method for assessing "value" by employing arbitrary budget caps, which inevitably results in a low estimate of value.

Detailed Discussion of Issues 1-3

1) The ICER cost-effectiveness model systematically underestimates CV risk, and is not directly applicable to the population most likely to receive PCSK9i's

The model used by ICER was intended to model CV risk in the entire US population (age 35-74) and was not designed for a high-risk population without extensive modification. In cost-effectiveness analysis, correct estimation of the magnitude of the risk (events) to be avoided is among the most critical inputs. Lack of transparency prevents replication of ICER's assumptions and results; however, tables in the ICER report suggest that it has modeled PCSK9i's in a lower-risk population, compared with the population that is defined in the FDA label and the population that Amgen has modeled in its cost-effectiveness analysis.

Table 17 of the ICER report shows that 201.6 million patient-years of treatment would be required to prevent 2.2 million major CV events over a 20 year period, or roughly 1% event avoidance per year of treatment. The American Heart Association's (AHA) 2015 Statistics cite the incidence of cardiac events in a population of patients with clinical atherosclerotic cardiovascular disease (ASCVD) as approximately 8% per year or 40% over 5 years.[4] If the CV event rate reduction seen with PCSK9i's approaches that seen in the recently published Navarese meta-analysis[5], this would imply 4% event avoidance per year, four times higher than what ICER assumes.

Further, when one compares the ICER-predicted risk with the risk seen in the active treatment arms of randomized clinical trials (RCTs) for statins in secondary prevention patients[6,7,8,9,10,11], the CV event rates seen in the RCTs were between 2 to 7 times higher than the ICER model events rates for the secondary prevention population. For example, the A to Z trial reports that the total major adverse cardiac event rate is 4 times higher than the event rate predicted by the ICER model. These published sources of event rates suggest that the ICER estimates for cost-effectiveness could vastly improve using evidence-based risk rate estimates.

ICER should also make transparent and justify the effect of other modeling assumptions which may currently bias the model against the benefits of LDL-C lowering, such as modeling LDL-C as a categorical variable instead of using a more appropriate continuous variable approach, or the effect of ignoring patients with baseline age 75 and over, now one the fastest growing segments of the American population. More than half of all cardiac events occur in patients aged 75 and over. [12]

Amgen has worked with clinical and economic experts to develop a cost-effectiveness model aligned with a model used by the National Institute for Clinical Excellence (NICE), a prominent health technology assessment (HTA) organization. This model assumes use in the familial hypercholesterolemia (FH) and clinical ASCVD populations, in line with the FDA label, and uses event rates that are calibrated accordingly. The model has been validated to appropriately predict the CV event rates seen in clinical trials and real world data and produces cost-per-QALY estimates that are significantly lower (*e.g.* PCSK9i's are cost-effective at current prices) than those produced by ICER. This model is currently undergoing peer review prior to publication and has been submitted to several national HTAs worldwide. We believe an appropriately calibrated CV Policy Model would confirm PCSK9i cost-effectiveness ratios of $150,000 or below, which is the ACC/AHA recommended threshold for value.[13]

2) The ICER model overestimates the population size that is likely to be treated with PCSK9i's

Referring again to ICER's cost-effectiveness modeling, the estimate of 201.6 million patient years of treatment over 20 years equates to an average of 10 million patients per year. Assuming the price used by ICER of $14,600, the average national expenditure for PCSK9i's in the US would be $146 billion dollars per year for every year out to 20 years. For perspective, $146 billion dollars is over a third of the entire US expenditure on all medications.[14] Such estimates garner headlines, but they do not encourage a balanced discussion about value or result in patient-centered decision-making.

The ICER analysis assumes a worst case scenario where there is no utilization management. Since such controls are common for biologics, this starting place is disconnected from the reality of the US health care system. The uptake of PCSK9i's will also be attenuated by the injectable route of administration, patient cost-sharing, expected adherence rates, and the typical uptake curve for new biologics. Further, renewed interest in statin optimization and the label requirement for maximally tolerated statins will also limit the eligible population. All of these factors must be taken into account when seeking to offer an accurate estimate of a new class of medicine's impact on drug cost, particularly when it may influence decision-making that impacts patient care.

We urge ICER to consider the history of statin uptake, the most relevant analog. In the first five years on the market, statins achieved 9% uptake.[15] After more than 10 years on the market, statin uptake in patients with high risk was ~23-30%, depending on the definition of high-risk.[16,17] Financial analysts confirm a balanced longer-term uptake of PCSK9i's (15% in ASCVD to 25% in FH).[18] All of these data sources taken together suggest a much lower uptake for PCSK9i's than ICER's 5-year uptake assumptions of 25% in the clinical ASCVD population and 75% in the FH population.

The rate of ezetimibe use is also instructive. Ezetimibe is a second-line therapy that reduces LDL-C, is indicated for a broader population then PCSK9i's, and now has CV outcomes results. The ICER model estimates average annual sales of ezetimibe equivalent to $24 billion per year over the next 20 years. This is in stark contrast to the 2014 annual sales of $1.8 billion. In fact, if the ICER model estimates are correct, ezetimibe sales should be higher than the peak sales of all statins combined.

In short, it is highly unlikely that the PCSK9i class will grow to the enormous expense predicted by ICER. The starting place for a balanced dialogue on value should take past experience into account and not begin with unrealistic worst case scenarios.

3) The ICER warning threshold for a drug's budget impact is not a meaningful method for assessing health system value and could undermine important health system priorities. Any value framework should consider long-term costs and include all patient-relevant aspects of value.

Critical US health system priorities include: 1) Addressing unmet medical needs that impact large populations, 2) Ensuring that the biopharmaceutical industry is productive and brings important innovative medicines to patients, 3) Encouraging health systems to invest more in interventions that work and less in those that don't across the entire healthcare sector, and 4) Ensuring that long-term value drives health system planning and investment.

Unfortunately, the new method proposed by ICER could undermine all four priorities as follows:

- **Significant Burden of Illness in Large Populations:** The new method penalizes medicines that address unmet needs in large populations of patients, the very conditions that degrade population health and increase health care costs.
- **Productivity:** The new method penalizes biopharmaceuticals for increased productivity: ICER-recommended growth and spending were determined by dividing permissible medicine spending growth by the average number of drugs approved.
- **Sector-wide, efficient resource allocation:** The new method discourages the efficient allocation of resources, only placing caps and growth limits on biopharmaceuticals and not on other aspects of the healthcare system. Budget caps have been repeatedly shown in research to reduce efficient healthcare delivery, diminishing patient access and outcomes.[19,20,21,22]
- **Long-term focus:** A five year budget focus is especially inappropriate to value treatment for chronic, long term illness.

The concept that value is determined by rationing the budget for individual new products has not been widely subjected to public input or review by health economists or policy-makers. The ICER budget impact method (mislabeled as "health system value")

proposes that drug growth and spending should be independently capped at no more than GDP growth + 1%. The negative effect of this artificial growth cap is compounded by other simplifying assumptions that create additional disincentives for drug development in the most important diseases that should be a national priority. ICER's model applies the same $900 million threshold for all new medicines regardless of the size of the population being treated by the medicine, and is not linked to the clinical importance or effect size of the particular medicine. Clearly, a disease such as CVD with large populations of sufferers is going to require far more treatment resources than less common diseases.

This system of allocation and rationing assures that many more budgetary warnings will be issued than are warranted, which could impact patient access to these important medicines for the patients in greatest need. For the PCSK9i's in particular, the ICER budget impact model projects that the sales of PSCK9i's in the five years after introduction will be more than $100 billion dollars. If ICER had assumed more realistic estimates of product uptake, and taken the larger impact of CV disease into account when allocating growth, it is unlikely that the incremental expense of PCSK9i's would have warranted any warnings. Artificially unaffordable estimates are the inevitable result of overestimations of drug uptake together with an arbitrarily low budget and no allowance for disease prevalence or broader aspects of long term value.

Finally, a five year estimate of a drug's costs and direct cost offsets is a payer finance metric, not a value metric. Short-term budget impact ignores some non-financial but critical aspects of value, such as the improved survival and avoidance of event-based deterioration of quality of life and productivity. The ICER "health system value" methodology is not a good metric for value because it ignores much of what patients and society consider value and focuses on the short-term financial interests of insurers.

Recommendations

Amgen recommends that the following changes be made to the final report before voting on questions is appropriate.

The event risk of the modeled population should be revised to be consistent with the known risk among high risk patients for whom the PSCK9i's are intended

For patients with clinical ASCVD, estimates of the risk of events range from 10% to 28% in the control arms of various clinical trials that studied such patients [23,24,25,26,27,28] and in patients with FH, the age-adjusted risk has been estimated to be 8-20 times greater than in patients without FH.[29,30] The ICER model should be calibrated to ensure consistency with events seen in clinical trials and ensure that the event rates apply to the appropriate high-risk patients. The methods and assumptions of these calibrations and other model parameters should be made transparent.

The estimates of the treated population should be revised to reflect a realistic scenario

The treated population should be revised to align with the current FDA approved label, *i.e*. "as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD, who require additional lowering of LDL-C." Utilization rates should be revised to reflect historical data for agents for similar diseases and include estimates of the effects of likely utilization management policies that are in place for many biologics. Statin and ezetimibe uptake patterns are a reasonable starting place, even though they may still overstate uptake because they have outcomes evidence, and utilization controls for PCSK9i's will presumably be more restrictive. Finally, assessments of lifetime drug cost should take into account rates of compliance based on analogs and include estimates of likely discounts.

Eliminate the arbitrary budget cap and the associated "value based price"

The budget cap is arbitrary and creates perverse incentives to develop new treatments that affect small rather than large numbers of patients irrespective of the unmet medical need. Pricing healthcare based on a drug expenditure cap rather than value leads to inefficient rationing of healthcare resources, and could undermine important health system priorities. ICER's "value based price" ignores the most important aspects of value and focuses primarily on short term financial costs. Any representation of value should include all societal and patient-relevant aspects of value such as event related mortality and deterioration of quality of life) and should consider long term costs and benefits of medicines.

Conclusion

A balanced and scientifically robust dialogue on value is a vital part of maintaining a focus on patient care, and making good choices in our dynamic health care system. Such dialogue must begin with estimates that are as accurate as possible using appropriate historical analogues and plausible, real-world assumptions. Equally important is publically available and transparent methodology and results, which ideally are peer-reviewed prior to introducing it publically as a potential platform for payer decision-making that could impact patient care. ICER's report on the value of PCSK9i's does not begin with these essential prerequisites, and therefore is an unsuitable starting point for a meaningful discussion until these deficiencies are remedied.

Amgen is committed to responsible pricing for our products, and an ongoing dialogue with patients, providers, payers, policymakers and regulators to finding ways to promote innovation, and alleviating the financial and societal burden of some of the world's most serious diseases. We look forward to a balanced, science-based dialogue about the value of PCSK9i's.

Sincerely,
Joshua J. Ofman, MD
Senior Vice President for Global Value Access and Policy, Amgen

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BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

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September 22, 2015

Institute for Clinical and Economic Review
One State Street, Suite 1050 (10th Floor)
Boston, MA 02109

To Whom It May Concern:

The Blue Cross Blue Shield Association (BCBSA) appreciates the opportunity to submit comments on the ICER draft report , titled *PCSK9 Inhibitor Therapies for High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks*.

BCBSA, a national federation of 36 independent, community-based, and locally operated Blue Cross and Blue Shield companies ("Plans") that collectively provide healthcare coverage for more than 105 million – one in three – Americans, applauds the new independently-funded ICER initiative to produce public reports regarding specialty drugs recently approved by the FDA. The reports, which include an analysis of the drugs' comparative effectiveness, cost-effectiveness, and potential budget impact, provide new information to policymakers and payers regarding the value to the healthcare system of these drugs.

The September 8, 2015, report includes a comprehensive review of currently available evidence on the newly approved PCSK9, providing valuable information to patients, payers, and providers regarding the effectiveness of the products relative to each other and to existing medications.

This ICER initiative to evaluate newly approved specialty medications is critical because spending on prescription drugs grew at a double digit rate of 13.1 percent from 2013-2014 in the US, to a total of $374 billion, before the PCSK9 inhibitors even hit the market. Most of that increase was due to new specialty drug products, including the new Hepatitis C drugs. This

report, and the reports from ICER to follow, adds an important contribution to the discussion of the sustainability of drug spending in the United States.

We thank you for your work. For questions regarding our comments, please contact Alexis Ahlstrom at alexis.ahlstrom@bcbsa.com or 202.626.8612.

Sincerely,

Justine Handelman
Vice President, Legislative and Regulatory Policy
Blue Cross and Blue Shield Association

The FH Foundation welcomes the opportunity to comment on ICER's Draft Report on Effectiveness, Value, and Pricing Benchmarks for PCSK9 Inhibitors for High Cholesterol, specifically as it relates to the population affected by familial hypercholesterolemia (FH).

The FH Foundation is a 501(c)3 non-profit patient-centered research and advocacy organization dedicated to improving the understanding, diagnosis, and treatment of familial hypercholesterolemia (FH) in order to prevent premature cardiovascular disease and improve patient outcomes in this high-risk population. The FH Foundation's CASCADE FH Registry is an important component of this effort and we have data to share that can help inform decision makers when it comes to accurately characterizing the FH population.

FH is an autosomal dominant genetic disorder that causes severely elevated LDL cholesterol from in utero and puts those affected at much higher risk for premature heart disease. FH is under diagnosed and under treated in the United States.

Many patients with FH are not able to reach safe levels of LDL-C, even on multiple therapies. There has been an unmet need for additional LDL lowering therapy for these individuals and we welcome the addition of PCSK9 inhibitors and other recently approved therapies to address that need. Our priority is to ensure that people with FH are diagnosed early and treated appropriately, including having access to the care they and their doctors decide is needed to address their risk.

The FH Foundation is concerned that some of the assumptions in the Report will negatively impact FH patient access to they care they need.

For the purpose of your analysis, we would like to highlight the following:

1. Recent studies suggest FH prevalence is approximately 1 in 250 for heterozygous FH[1] and 1 in 160,000 for homozygous FH[2], rather than the 1 in 500 and 1 in 1 million cited in the Report.
2. Currently, fewer than 10% of individuals with FH are diagnosed in the United States[3].
3. We do not agree with the definition of the heterozygous FH population as individuals with LDL-C over 250 mg/dL untreated and over 200 mg/dL with statin treatment. A clinical diagnosis can be made based on an LDL-C over 190 mg/dL in adults and over 160 mg/dL in children, along with a family history of

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CVD[4]. Most experts would consider a lower level of LDL-C to suggest possible FH in a person with a family history of known FH. A cut off of 250 mg/dL without statin treatment and 200 mg/dL with statin treatment, as stated in the Report, would miss many people at high risk of CVD due to FH.

4. The risk of CVD associated with FH is not only due to extremely high LDL-C levels, but also to the years of exposure[5].
5. Heart disease strikes early for FH, affecting men, women, and even children early in life. Left untreated, men with heterozygous FH have a 50% chance of coronary heart disease by age 50 and women have a 30% chance by age 60[6].
6. The model presented in the Report is of the adult population aged 35 to 74. Unfortunately, individuals with FH are affected earlier in life. This model would not show the benefit of early optimal treatment. The impact of FH can be seen as early as 12 years old, when comparing CIMT results of FH and non-FH siblings[7]. Diagnosis and treatment must start early.
7. A five-year time frame for FH is not adequate to see the benefits of treatment for FH.
8. Left untreated, FH patients in general have a 3-4 times higher risk for CHD compared to unaffected subjects, and CHD events occur one decade earlier[8].
9. FH patients have higher rates of coronary heart disease, as represented in the CASCADE FH Registry population: Prior CABG, 13.8%; Prior MI, 12.4%; Prior PCI, 17%[9.]
10. We do not agree that LDL-C of 160 mg/dL is an appropriate goal for individuals with heterozygous FH. An appropriate LDL-C goal for individuals with FH is a target range of 70-100 mg/dL or lower. A goal of 160 mg/dL, as stated in the Report, leaves people at undue risk for CVD given their prolonged exposure to very high LDL-C.
11. For portions of the FH population, treatment strategies would likely include statins, ezetimibe *and* PCSK9 inhibitors, if needed, rather than ezetimibe *or* PCSK9 inhibitors as modeled in the Report.

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[4] Hopkins, PN, et al. Familial Hypercholesterolemia: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011; 5: 59-517.

[5] Risk of fatal coronary heart disease in familial hypercholesterolemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303(6807):893-896.

[6] Marks D, et al, A review on the diagnosis, natural history, and treatment of familial hypercholesterolemia. Atherosclerosis 2003; 168: 1-14.

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[8] R. Huijgen, I. Kindt, J.C. Defesche, J.J.P. Kastelein, Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29,365 individuals tested for 64 specific low-density lipoprotein-receptor sequence variants., Eur. Heart J. 33 (2012) 2325–30. doi:10.1093/eurheartj/ehs038.

[9] O'Brien EC, deGoma EM, Moriarty PM, Linton MF, Shapiro MD, Duell PB, Ballantyne CM, Neal WA, Ahmad ZS, Duffy D, Hudgins LC, Hemphill LC, Underberg JA, Watson KE, Gidding SS, Baum SJ, Wilemon KA, Pickhardt D, Kindt I, Rader DJ, Roe MT, & Knowles JW. Initial Results from the CASCADE-FH Registry: CAscade Screening for Awareness and Detection of Familial Hypercholesterolemia. Clinical Cardiology 2015 & JACC 2015.

12. The model assumes that "all patients who met the operational definition of FH…received incremental therapy (p.ES10)." Currently, fewer than 10% of individuals with FH are diagnosed. In addition, not every person with FH will need a PCSK9 inhibitor. Many can reach LDL goals on previously available therapies.
13. However, many patients with FH cannot reach optimal LDL-C levels, highlighting the unmet need for additional options. Even with treatment at leading lipid clinics in the United States, the median LDL-C achieved by patients in the CASCADE FH Registry is 143 mg/dL[10].
14. The patient-level burden of illness is very high for FH. FH has an impact on the quality of life for affected individuals, in addition to cardiac events. The CASCADE FH Registry finds that more than half of patients diagnosed with FH are burdened with anxiety associated with their risk for early heart attacks and premature death[11]. Individuals with FH are painfully aware of their risk due to the fact that premature heart disease runs in FH families.
15. While the report states that "differences in CVD risk are less marked between patients with HeFH and those with a prior history of CVD who have elevated LDL-C levels despite other treatment" (p.ES7) this statement does not take into account that a disproportionate number of people with CVD have FH and are undiagnosed. Importantly, it does not consider the advantage of potential primary prevention to avoid CVD for individuals with FH. There is an inherent benefit to primary prevention of CVD events.

Better LDL-C management promises to improve patient outcomes for individuals with FH. Given the high cost, both financial and otherwise, of premature cardiovascular disease, this population must be proactively and adequately treated. FH is known to dramatically increase the risk for early heart disease. It can be detected in childhood when there is still time to prevent the development of atherosclerosis. Diet and lifestyle management will never be enough for this population, as important as it is. Pharmacological therapy is almost always necessary. Our goal is primary prevention of atherosclerosis in patients with FH to prevent heart attack, stroke, the need for revascularization, and premature death. It is not enough to prevent the second heart attack once CVD has been established. Our goal must be to diagnose and treat FH in order to prevent the first heart attack so people with FH can live longer, healthier lives.

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[10] O'Brien EC, deGoma EM, Moriarty PM, Linton MF, Shapiro MD, Duell PB, Ballantyne CM, Neal WA, Ahmad ZS, Duffy D, Hudgins LC, Hemphill LC, Underberg JA, Watson KE, Gidding SS, Baum SJ, Wilemon KA, Pickhardt D, Kindt I, Rader DJ, Roe MT, & Knowles JW. Initial Results from the CASCADE-FH Registry: CAscade Screening for Awareness and Detection of Familial Hypercholesterolemia. Clinical Cardiology 2015 & JACC 2015.

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Comments on ICER assessment of PCSK9

Dear Dr. Pearson, et al.,

Thank you for the opportunity to comment on the ICER review on PCSK9 inhibitors. We have found it to be, for the most part, accurate and rigorous. However, we have identified some issues with the overall methodology, which will be addressed by industry-wide organizations such as NPC. We will limit our comments to those concerning our own product, ezetimibe.

- On page ES4, the report states that the meta-analysis by Navarese "provided the basis for many of the findings in this review." We believe that the limitations of this meta-analysis, in particular the results around clinical event outcomes have not been appropriately represented in the ICER report. While the meta-analysis may indeed be of high quality, the resulting conclusions do not constitute strong evidence under the GRADE or any other methodology for rating the strength of conclusions. Strength of evidence depends not only on the quality of the meta-analysis, but on the quality of the studies being assessed. The RCTs included in Navarese's analysis are not designed to assess clinical outcomes and the data were derived from a very small number of events. Neither study design nor consistency of outcome are sufficient to support a strong conclusion. We request that these limitations be re-emphasized in the ICER report.

- The report contains some inconsistent data on ezetimibe with respect to the LDL efficacy when added to ongoing statin therapy. On page 6 the document references two analyses in which the LDL-C reduction of ezetimibe post-statin and as monotherapy are 23.6% and 18.6% respectively. The estimate for monotherapy given in Table 10 on Page 32 is consistent with page 6, however the incremental effect of ezetimibe on top of statin is substantially different; 13.94% versus the 23.6% reported on page 6. The 13.94% estimate comes from Figure 1 on page 25 of reference 118. This estimate is based upon a change from a pre-statin LDL-C baseline. In contrast, in the cost-effectiveness analysis in reference 118 the actual adjusted LDL-C reduction that was utilized was 22.4% (Table 30, pg. 52). This value, which utilizes the appropriate baseline, is consistent with the 23.6% reduction noted in reference 31 and is also consistent with a pooled meta-analysis of ezetimibe trial data conducted by Morrone et.al. 2012[1] in which LDL-C reduction when co-administered with statin was 23.4%. The difference between ezetimibe LDL-C efficacy based upon a pre and post-statin baseline is explained on page 52 and figure 6 of reference 118.

  The appropriate LDL-C value to use in the cost effectiveness analysis for ezetimibe from reference 118 is 22.4%, not the 13.94% reported in Table 10. The current analysis undervalues ezetimibe considerably. We therefore request that Table 10 be revised to include the correct value for ezetimibe co-administered with statin, and any subsequent

analyses that were made using the 13.94% value be repeated and reported using the 22.4% value.

- The base case for the cost-effectiveness analyses uses a 20-year timeframe. For chronic therapies like cholesterol modifying treatments it is recommended to use an appropriate time horizon for such evaluations[2,3]. A 20 year time horizon will significantly underestimate the value of treatment especially for younger patients where cost and benefits will only be accrued up to age 55 or 65 in the case of patients 35-45 years old. The tornado plot on page 38 illustrates this point. When the time horizon is increased by 10 years to 30 years ICERs are reduced from $681,000 /QALY to a little over $400,000/QALY . This suggests that there is a substantial amount of value not being accounted for with a 20-year time horizon. We typically conduct our evaluations to a maximum age of 100 rather than a specific time horizon. We recommend that ICER expand their cost-effectiveness analyses to incorporate a much longer timeline.

- There are limited details in the draft report on the estimation of the baseline risk of CVD events and no sensitivity analyses are provided in the document with respect to uncertainty around baseline risk. In other CVD models[4], sensitivity analyses conducted with respect to baseline CVD risk have shown that baseline risk estimation has a significant impact on ICER results due to the fact that life expectancy is highly influenced by event risk. It would be beneficial if sensitivity analyses with respect to baseline CVD risk were included in the report.

- The price for ezetimibe used in the cost-effectiveness analyses is the current wholesale acquisition cost, however there is no mention of the fact that ezetimibe will be going off-patent towards the end of 2016. Consequently, the lifetime costs associated with ezetimibe treatment will be significantly overestimated. Given this fact, scenario analyses should be included to assess the impact of changing prices of ezetimibe on lifetime costs of treatment.

- In addition to our objections to some of the decisions made during the course of the cost-effectiveness analysis of ezetimibe, as described above, we question whether it is appropriate to perform such an analysis on a product that is not the subject of the current review. The subject of the review is PCSK9 inhibitors and it does not capture the full universe of data available on ezetimibe. Thus, conclusions drawn regarding ezetimibe are of limited value. Moreover, the Voting Questions presented to CEPAC address only the Net Health Benefits of Ezetimibe, not its Care Value or Health System Value. That being the case, we question the utility of performing a cost-effectiveness analysis of ezetimibe.

  Having performed such an analysis, ICER then failed to go on to calculate value-based

benchmark prices for ezetimibe. We consider this to be misleading, as we believe that the value-based benchmark prices for ezetimibe, if calculated using the appropriate values as discussed above, would be far more similar to the prices actually paid by CEPAC members than prices paid for PCSK9 inhibitors. If ICER believes they must persist in reporting the results of their cost-effectiveness analysis for ezetimibe, we strongly request that they first revise their calculation as described above, and then go on to perform an analysis of value-based benchmark pricing.

- Finally, buried on page 52 of the review is an acknowledgement that "It is plausible that adherence to PCSK9 inhibitors… may be lower in the real world compared with that observed in clinical trial populations." We believe that it is not merely plausible, but extremely likely that adherence will be reduced in the real-world population. Therefore we request that this point be emphasized more strongly, and appear both in the Executive summary of the revised document and in the presentation to CEPAC scheduled for October 2015.

Sincerely,

Richard Chapell
For the Merck Ezetimibe Comment Team

References:

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Re: Draft Report - PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks

Dear ICER Panel Authors,

The following comments are provided on behalf of the National Lipid Association (NLA), a nonprofit, multidisciplinary medical society focused on enhancing the practice of lipid management in clinical medicine. We are responding to the Institute for Clinical and Economic Review (ICER) draft report entitled "PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks" (the "Report") and the Draft Questions for Deliberation.

The Report purports to address the following questions:

1. What evidence exists to support decisions regarding risks and benefits of initiating PCSK9 inhibitor therapy?
2. Are there specific populations in whom the benefits of PCSK9 inhibitors outweigh the risks?
3. If therapy is considered, what is the potential cost effectiveness and budgetary impact of different strategies to target therapy?

The NLA agrees with the draft ICER report, which indicates that based on the available evidence PCSK9 therapies provide a "substantial or incremental net health benefit" for patients with familial hypercholesterolemia, established cardiovascular disease, and high risk for cardiovascular disease on maximally-tolerated statin therapy, who need additional lowering of atherogenic cholesterol (LDL-C and non-HDL-C). Based on the existing evidence, PCSK9 inhibitors provide an additional 50-66% reduction in LDL reduction beyond statin therapy in addition to improving other lipid parameters. Upon completion of the major outcomes trials, more data will be available on patient tolerance and adverse incidence, but based on the evidence available today, the NLA contends that the benefits of PCSK9 inhibitors outweigh the risks in the identified specific populations.

While we generally agree that a reasonable acquisition cost is always beneficial, the NLA, as an organization, is not in a position to provide comment on the cost effectiveness and budgetary impact of this therapy.

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The NLA appreciates ICER's use of the NLA's definition of statin intolerance in the Draft Questions for Deliberation and hopes ICER continues to utilize the definition as its moves forward with payers and stakeholders.

Sincerely,

Carl E. Orringer, MD, FNLA
President

Terry A. Jacobson, MD, FNLA
Chair, Science & Policy Council

Dean A. Bramlet, MD, FNLA
Chair, Practice Management Council

Peter H. Jones, MD, FNLA
Chief Science Officer

Pfizer response to ICER draft report: 'PCSK9 inhibitors for the treatment of high cholesterol: effectiveness, value, and value-based price benchmarks'

Pfizer welcomes the opportunity to comment on the results of the ICER draft report, and ICER's effort in evaluating the available evidence to improve patient outcomes and help foster a collaborative approach to generate a more effective and efficient health care system.

Pfizer believes it is important to establish a broadly validated approach using the most appropriate methodologies for evaluating the *Care Value* and *Health System Value* of any new medicine or device. This is an essential step in increasing the likelihood that results are robust, accurate and not misleading or arbitrary. Presentation of the methodology, inputs, and results should follow accepted guidelines (CHEERS[i]) to allow scrutiny of the model results; this applies particularly to provision of input parameters and modeling of uncertainty.

A. Economic evaluation

Patient population in the model should be aligned with Prescribing Information (USPI) for approved PCSK9 inhibitors (PCSK9i's):

In the ICER draft report, the subpopulations studied are: 1) FH patients; 2) ASCVD statin intolerant patients; and 3) ASCVD patients on statin therapy with a LDL-C ≥70mg/dl.

These subpopulations are not aligned with the prescribing information for currently approved PCSK9i's in the United States. PCSK9i's[ii] are currently not indicated for statin intolerant patients. Given the uncertainty around impact on CV outcomes pending ongoing trials and given the current labeling of these products, PCSK9i cost effectiveness should be estimated only in two subpopulations: FH and ASCVD patients on maximally tolerated statin therapy (not on any statin, e.g. low intensity statin) requiring additional LDL-C lowering.

Since the USPIs do not specify what 'additional LDL-C lowering' means, sensitivity analyses should be performed on different LDL-C thresholds (e.g. obtaining expert opinions for threshold values, e.g. LDL-C ≥100 or ≥130mg/dl).

ICER modeled the entire US population aged 35 to 74. Although there is limited evidence on the efficacy and safety of statins and PCSK9i's on patients aged 75 and older, PCSK9i's are indicated for all adults. The aim of an economic model should be to model the population eligible for a new treatment mimicking as closely as possible the population of interest. US epidemiology data shows that ASCVD prevalence increases with age[iii], while FH patients tend to be diagnosed at a younger age. Patient subpopulations should be stratified by baseline LDL, CVD risk by age and gender, and background therapy.

Treatment strategies should consider inclusion of statin + ezetimibe +PCSK9i: Three treatment strategies were modeled in patients able to tolerate statins: 1) statin; 2) statin + ezetimibe and 3) statin + PCSK9i. Until the PCSK9i CV outcomes data are available, the potential treatment strategy of statin + ezetimibe+PCSK9i should also be compared to statin+ ezetimibe given the results of the IMPROVE-IT trial.

***The model time horizon should be lifetime*:** The time horizon of the ICER model is 20 years; but PCSK9i's treat chronic conditions and a lifetime horizon should be considered.

The results of the Meta-Analysis require validation and sensitivity analyses: The meta-analysis ICER performed to supplement the Navarase et al. met-analysis combined data from 41 phase 2 and phase 3 clinical trials (which were not powered for CV outcomes) on two different PCSK9i's, with different dosing regimens, different follow up time, different subpopulations, and different background therapies. This approach was preferred to overcome the hurdle of having too few events to estimate major adverse cardiac events (MACE). The analysis did not

apply stratification to evaluate the patients for which PCSK9i's are indicated in order to correct for potential biases. The meta-analysis included clinical trials evaluating PCSK9i as monotherapy, for statin intolerant patients, and for primary prevention patients, although these usages are not included in the products' USPIs. Furthermore, the results of the meta-analysis on the effect of PCSK9i's on CV outcomes vs. statin and vs. ezetimibe are not reported.
Quoting the USPIs, the effect of PCSK9i, "*on cardiovascular morbidity and mortality has not been determined*". Extensive sensitivity analysis should be considered (including the extensive literature on the association between LDL reduction and CV events from statin trials and the IMPROVE-IT trial) to validate the results of the meta-analysis.
The model estimates "the degree of LDL-reduction with PCSK9i when used alone or in combination with statins" (PCSK9i's are not indicated as monotherapy). The assumption that the drugs are equally efficacious in all populations and that the reduction in LDL cholesterol from baseline was constant across all subgroups studied requires supporting evidence.
CV outcomes used in the economic evaluation must be revaluated once the CV outcomes trials are available to reduce the level of uncertainty on the added value of PCSK9i on the patient treatment pathway and to most appropriately inform decision-making.
***Drug costs used in the model should have sensitivity analysis*:** The cost-effectiveness model uses the whole sale acquisition price of one PCSK9i of $14,600. However, this likely does not accurately reflect available discounts and rebates. Wide sensitivity analysis with different price discount levels should be considered.
The results of the cost-effectiveness analysis are conditional on the model selection. Although the CVD policy model is a validated prevention model, it has not been validated for the assessment of new medicines, and different lines of therapies.
***ICER ezetimibe model results differ from results published in peer reviewed journals*.** The results of the ICER cost effectiveness analysis show that PCSK9i+ statin therapy and ezetimibe + statin therapy are not cost effective when compared to statins alone in the 3 subgroups studied. The ezetimibe cost-effectiveness results conflict with studies published in peer-reviewed journals[iv]. Additionally, various Health Technology Assessment agencies have evaluated ezetimibe with favorable results. NICE[v] appraisal shows that ezetimibe is cost-effective with costs per QALYs ranging from £8000 to £50,000 depending on the treatment strategy used and the population analyzed.
The departure of ICER's results (ranging from $226,000 to $373,000 costs per QALYs) from the results of all the published ezetimibe cost-effectiveness analysis suggests the ICER model lacks external validity. Further validation will facilitate the interpretation and acceptance of the PCSK9i results vs standard of care.

B. Methodology of the Budget Impact Model

Pfizer recognizes the importance of balancing affordability with bringing innovative medicines to market. We believe that the approach taken by ICER to estimate the national budget impact and the corresponding value-based prices do not reflect important considerations. First, the assertion that healthcare spending must be tied to GDP growth ignores the built in cost containment across the lifecycle of pharmaceuticals related to patents and generic competition. Second, the assumption that new drug spend should be equally spread across all new molecular entities (NME) ignores several aspects of unmet needs, burden of disease and drug utilization. Specifically, follow-on approvals for medications expanding the indicated populations are not included in NME approvals nor is there consideration for the varying sizes of indicated

populations across all newly approved products. These limitations bias against new products that address larger populations with substantial unmet clinical need and favor products that initially treat small populations.

Thus, Health System Value (HSV) threshold prices may create disincentives to develop innovative treatments for large populations with unmet need. Not all drugs represent equal cost offsets or reductions in avoidable mortalities and morbidities. *HSV* calculations assume there should be much more limited differences across drugs in the proportion of spending growth they consume.

Moreover, although 5-year budget impact horizon for *HSV* price thresholds may be appropriate for certain therapies it likely is not appropriate for PSCK9i given the clinical guidelines focus on CV risk scores calculated as a 10 years risk. **The 5-year budget impact horizon does not accurately reflect long term benefits of preventive therapies**.

The result of the ICER effort in evaluating the available evidence could be seen as a simplistic pricing answer to a much more complicated drug spending and management situation. The *HSV* price benchmark of $2,177 has attracted the exclusive attention of the press with no mention of other key dimensions of treatment, and/or limitations of the analysis and methodology. A $2,177 price for PCSK9i's is problematic in a number of ways, both methodological, as described, as well as conceptually. Specifically, the rationale as to why PCSK9i's should be priced lower than ezetimibe (which has been accepted as a cost-effective therapy), when PCSK9i's have demonstrated greater efficacy in lowering LDL-C is unclear and again reflects a lack of validity with the approach.

Since the ***budget impact results are conditional on the results of the cost-effectiveness analysis*** and on the various assumptions used in the model, the populations and the inputs represented in the budget impact analyses are similarly inappropriate.

For this analysis to be more conducive to promoting health improvements as a contributor to general economic welfare and growth there is a ***need to create a robust, unbiased, and fully transparent methodology*** to validate the economic impact of new therapies that also takes into consideration the fragmented nature of the US healthcare system.

C. <u>Voting questions-</u>

ICER should clarify how different components are weighted in the overall determination of 'high', 'intermediate' and 'low' in the provisional *Care Value* and *HSV* of a new medicine.

We would also recommend ICER consider adding the following questions:

- Are the results of the ICER cost-effectiveness analysis robust enough to reach a consensus decision regarding the *Care Value* of the PCSK9i class?
- Are the results of a meta-analysis based on ad hoc analysis and LDL phase 2 and 3 trials which were not powered to assess CV outcomes, accurate and robust enough to determine the long term effect of PCSK9i on CV outcomes and safety?
- Should the PCSK9i class *Care Value and Health System Value* be re-evaluated once the outcomes data becomes available?

Respectfully submitted,
09/22/2015

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[ii] Alirocumab US prescribing information: Alirocumab is a PCSK9 inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. http://www.regeneron.com/Praluent/Praluent-fpi.pdf Evolocumab US prescribing information: Evolocumab is a PCSK9 inhibitor antibody indicated as an adjunct to diet and 1) maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol (LDL-C); 2) other LDL-lowering therapies in patients with HoFH who require additional lowering of LDL-C. http://www.multivu.com/players/English/7414054-amgen-repatha-fda-approval/links/7414054-repatha-pi-hcp-english.pdf

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Sanofi and Regeneron welcome the opportunity to comment on the *ICER Draft Report on PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks*.

In summary, we have concerns with the report, which center upon three key domains:

1) ***Limitations in methods and assumptions***. There are limitations in the Care Value analysis, resulting in likely underestimation of cardiovascular disease (CVD) risk in approved patient populations for the PCSK9 inhibitor class and undervaluation of the potential clinical and economic benefits of these medications. Additionally, variations in key inputs can cause large swings in model outputs.
2) ***Inadequate visibility into the model architecture***. This results in the inability to fully interpret and validate conclusions. Peer review of the model is desirable.
3) ***Imposition of a narrowly focused Health System Value analysis***. This analysis includes unrealistic estimates of budget impact and establishes arbitrary investment thresholds for societal investment in novel pharmaceuticals and ignores the value and risk of innovation.

Sanofi and Regeneron are committed to developing innovative medicines that make a difference in patients' lives and ensuring that patients in the U.S. who are prescribed alirocumab are able to access the medicine and receive the support they may need.

We believe alirocumab provides meaningful value to those patients with the greatest unmet need, and carefully considered multiple parameters in establishing an appropriate price for alirocumab. It is also important to consider that specialty biologics require unique manufacturing & supply chain, together with intensive patient and physician support models, neither of which are included in the cost-effectiveness analysis.

We agree with the conclusions of the Comparative Clinical Effectiveness analysis that PCSK9 inhibitors provide substantial or incremental net health benefits while being well tolerated for all relevant patient subpopulations. We also agree with the statements that "the drugs improve intermediate risk factors for cardiovascular disease" and "substantially reduce LDL-C, total cholesterol, lipoprotein(a), and modestly elevate HDL-cholesterol."

However, we disagree with certain aspects of the modeling assumptions that drive the outputs of the analysis. We are confident in the clinical and economic value that alirocumab contributes to the PCSK9 inhibitor class. We believe appropriate patients should have broad access to innovative medicines. As one input for determining an appropriate price for alirocumab in the U.S., we evaluated the potential value of treatment in our indicated populations. Utilizing our cost-effective modeling approach, for patients with clinical astherosclerotic CVD (ASCVD) and those with heterozygous familial hypercholesterolemia (HeFH), we made efforts to ensure that the net price of alirocumab to payers is cost effective.

Taken together, these limitations in the ICER approach raise significant concerns about the conclusions of the report. Below, we outline our concerns in greater detail.

1. <u>Limitations with Methodology and Assumptions</u>: The benefits associated with the PCSK9 inhibitor class are underestimated in the intended patient populations in the three key areas highlighted below: 1) cardiovascular (re)event rates among CVD patients and its association with LDL-C at baseline; 2) the lifetime risk profile for the familial hypercholesterolemia (FH) population; 3) the age distribution in the model.

Recommendation: *Provide detailed descriptions of all data sources, assumptions and model input values with sources, and a complete description of the CVD Policy Model methodology.*

a. Risk groups are defined using wide baseline LDL-C categories that underestimate the CVD risk faced by patients with higher levels of LDL-C within a given category. This is important because baseline LDL-C level is a key driver of CVD risk and ultimately of cost effectiveness estimates.

ICER's analysis groups patients into one of three LDL-C categories: LDL-C <70 mg/dL, LDL-C between 70 and 99.9 mg/dL, and LDL-C ≥100 mg/dL. The third category is particularly broad toward the lower end of distribution. Since LDL-C as a risk factor enters the model categorically rather than continuously, the risk for CVD at baseline will be constant within each category. This is a restrictive assumption since CVD risk is increasing in LDL-C levels, and the assumption is particularly worrisome for the third category given the high variance of risk for the population within the category. ***Recommendation:*** *Add discrete categories above 100 mg/dL.*

b. Using LDL-C values alone as the proxy definition of FH significantly underestimates, the lifetime CVD risk profile of the FH population.

The ability to identify FH patients in databases is difficult and the approach taken is reasonable; however, it is unclear how the probability of the incident and subsequent CVD events are determined. FH patients tend to have earlier and more frequent CVD events and higher CVD mortality rates compared to non-FH populations with similar LDL-C levels [10, 11] due to lifetime exposure to high LDL-C [12]. ***Recommendation:*** *Framingham risk estimates are not appropriate to estimate CV risk in FH patients. Further analyses should be undertaken using published standardized mortality ratios between FH and non-FH populations [11] to allow for the true mortality effects in the FH group.*

c. A significant underestimation of deaths and CVD events averted by PCSK9 inhibitor use in the risk groups studied may be due to the inclusion of a younger lower risk population and truncation of the older age groups who are at highest risk of having a first or recurring CVD event.

The age distribution in the CVD Policy Model skews young, which ignores potentially large treatment benefits to the population over age 75. The baseline model cohort includes only individuals aged 35-74. The age distribution is particularly problematic since there are only half the number of 75-84 year olds that would be in a cohort that began with a representative population of 35-84. This is why a lifetime model would be preferable to truly represent the benefits of interventions such as PCSK9 inhibitors. The 2010 National Vital Statistics Report on mortality shows that 62% of CVD deaths occur in those aged 75+ [13, 14], suggesting that the absence of individuals in older age groups results in underestimation of potential benefits from PCSK9 inhibitor treatment compared to a natural cohort, or a life-course model. [15-17]. ***Recommendation:*** *A lifetime model should be applied to a cohort representative of the U.S. age distribution to reduce risk underestimation. If the model architecture requires defined age cut-points (35-74 years), ensure the age distribution does not change over the 20 year period and that the upper age cut-off is at least 84 years.*

2. <u>Inadequate Visibility to the Model Architecture.</u> Transparency around the Markov model architecture and assumptions is critical to interpreting results in context. In this report, readers are left to infer model details related to the estimation of CVD risk in the secondary prevention population, one of the important target populations for PCSK9 inhibitors. The CVD Policy Model presents parameters for individuals with prior CVD events, but ICER's comparative value appendix discusses calculation of heart disease and stroke based on the Framingham Heart Study. It is unclear whether values from Framingham are applied to the entire model population,

but the limitations of Framingham data in this context have been highlighted by ACC/AHA.[1] The risk profile for the ASCVD population should utilize event probabilities associated with an ASCVD population.

Despite the reference to the original CVD Policy Model publication, [2] the ICER report still has considerable information gaps. The report lacks detailed summary statistics and sample sizes for age, sex, and the 8 CVD risk factors, which makes the baseline population characteristics indeterminable. Moreover, without a baseline reference point, especially with respect to key parameters such as baseline LDL-C distribution, it is difficult for readers to put the results into context. In addition, missing relevant life tables make it difficult to understand the source of life years gained, which is critical because the results in appendix 7, tables 3 and 4 imply that an average of 6 life years are gained from a death averted. This is half the size of similar estimates in other published literature – for example, the recent U.S. burden of disease report from the Institute of Health Metrics and Evaluation estimates values closer to 12 life years [3].

A wider understanding of these assumptions is essential to testing the validity of results. For example, we compared the report's calculated incremental cost-effectiveness ratios for ezetimibe against a wider literature. While the ICER report estimates a cost per QALY value of $373,000 for ezetimibe plus statin therapy for secondary prevention patients, multiple published peer-reviewed international cost-effectiveness studies cite cost per QALY values ranging between $20,000 and $60,000 in 2015 USD [4-9]. This suggests that the ICER model is estimating considerably higher costs per QALY gained compared to other studies. ***Recommendation:*** *Provide further information on the CVD Policy Model, include life tables in the appendixes, and provide clarification on rationale for QALY assumptions*.

3. <u>Imposition of a Narrowly Focused Health System Value Analysis</u>. The 'new drug' thresholds suggested by ICER are based on unreliable assumptions and unrealistic estimates of uptake that significantly overestimate the budget impact, creating a chilling effect on innovation and disincentives for healthcare investment. Results from this section should be de-emphasized since they do not consider the benefits to patients.

The health system value analysis, which drives ICER's budgetary recommendations, focuses on drug cost, not value, and the "GDP+1" approach uses arbitrary thresholds that are subject to measurement error. Caps on pharmaceutical spending separate the assessment of total cost from the more relevant assessment of net benefit to patients, which can lead to erroneous decision-making, because low cost is often a poor measure of value. The approach outlined by ICER sets a budget threshold of $904 million in total annual costs for a new drug. Applying this threshold to past innovations, such as statins and anti-retrovirals, would have limited access to these drugs at the time they were introduced to the market [18, 19]. The underlying logic of a cap is flawed if only applied to one health care component

Further, the uptake levels used for the analysis were 10%, 25%, 50%, and 75% after 5 years. In contrast, a recent study examining retrospective uptake of statins [18] showed that after 20 years, the uptake in the U.S. amongst those in the statin benefit groups had reached just 16%.

ICER's analysis ignores important differences between the wholesale acquisition price (WAC) and the effective price in U.S. settings. WAC price does not accurately reflect discounts and may bias estimates. ***Recommendation*****:** *Allow for a GDP growth range, number of new drug approvals, and more realistic uptake rates for an injectable medication. Sensitivity analyses should be conducted to incorporate a range of estimates on discounts offered to plans and co-pay assistance to patients in evaluating value based pricing*.

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