COVERAGE WITH EVIDENCE DEVELOPMENT & ADAPTIVE LICENSING:

TWO SIDES OF THE SAME COIN?

WORKSHOP SUMMARY

February 2012
Project Staff
This workshop was hosted by the Center for Medical Technology Policy (CMTP) and Massachusetts Institute of Technology’s (MIT) Center for Biomedical Innovation (CBI) NEWDIGS program (New Drug Development Paradigm) on November 8th, 2011 in Baltimore, MD. Key project staff are listed below:

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Acknowledgements
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About Center for Medical Technology Policy (CMTP)
The Center for Medical Technology Policy (CMTP) was established as an independent non-profit 501(c) (3) organization in January 2008 in order to improve the quality, relevance, and efficiency of health care research. We focus on the design and implementation of comparative effectiveness research to produce information that helps patients, clinicians, and payers make informed treatment and policy decisions. CMTP was established to provide a forum in which these decision-makers could play a meaningful and sustained role in all aspects of health care research, in hopes of generating better information about the comparative benefits, risks, and costs of health interventions.

Located in Baltimore, Maryland, CMTP conducts its work by fostering multi-disciplinary collaborations that include academic institutions, patient advocacy organizations, health professional organizations, public and private health plans, life sciences companies, and federal and state government agencies.

About NEWDIGS
The NEWDIGS (New Drug Development Paradigm) program, led by the MIT Center for Biomedical Innovation (CBI), is a unique collaboration for transforming the global healthcare innovation system to deliver greater value to all stakeholders and to ensure its sustainability. The NEWDIGS collaboration model involves strategic coordination of “real world” demonstration projects with cross-disciplinary academic research in science, engineering, management, and clinical medicine, led by MIT and the Harvard-MIT Division of Health Sciences and Technology (HST). This systems approach enables rapid cycle learning in the testing, validation, and continuous improvement of interdependent transformational “levers” in technology, process, and policy designed to accelerate our collective capacity to diagnose, treat, and prevent disease. NEWDIGS participants include senior leaders in biopharmaceutical firms, regulators, payers, providers, patients, and other key stakeholders from the global healthcare industry.
**Overview**

There is currently a gap between the evidentiary standards required by regulatory agencies and payers for assessing the benefits and risks of a therapeutic. This gap often delays access for patients to new, high value treatments; compromises the quality of our knowledge about new products; and increases risks and uncertainties associated with the innovation process. Innovative approaches to both regulatory and reimbursement policy such as Adaptive Licensing (AL), and Coverage with Evidence Development (CED), respectively, if designed and implemented jointly, have the potential to bridge this gap.

The Center for Medical Technology Policy (CMTP) and the NEWDIGS (New Drug Development ParadIGmS) program, led by the MIT Center for Biomedical Innovation (CBI), convened this workshop to explore potential approaches to integrate AL and CED, two traditionally distinct areas of pharmaceutical policy. This was done through a structured discussion and brainstorming with stakeholders (Appendix 1) in representative roles to explore the benefits, risks, challenges and possible solutions of integrating regulatory policies such as AL and reimbursement policy schemes such as CED, on healthcare delivery. To these ends, the workshop aimed to:

- Describe recent thinking on AL and CED.
- Summarize lessons learned from previous experience with elements of adaptive drug licensing programs in the United States, Canada and the European Union and with adaptive regulation in other areas.
- Summarize lessons learned from previous experiences with implementation of CED by public and private payers in the United States and other countries.
- Identify regulatory, reimbursement, methodological, operational, financial and other challenges to coordinated implementation of AL and CED using case studies and develop approaches to address these challenges.
- Discuss opportunities for research and/or pilot projects to further evaluate the integration of adaptive licensing and CED.

**Coverage with Evidence Development (CED)**

Once a therapeutic is approved by regulatory agencies, coverage is a dichotomous “yes/no” decision guided by ‘reasonable and necessary’ under Medicare and ‘medical necessity’ by private payers. The working definition for “reasonable and necessary” is that there should be adequate evidence to conclude that the item or service improves health outcomes. The challenge with this definition is that adequacy of evidence required by payers is subjective and often different from the evidentiary requirements of regulatory agencies. Payers are more interested in measuring health outcomes experienced by patients as compared to measuring outcomes such as surrogate endpoints. In addition, expensive biologics and devices are raising the threshold of evidentiary standards required by payers to provide coverage for new technologies.
Coverage with Evidence Development (CED) is a form of conditional reimbursement for medical technologies characterized by restricted coverage for patients enrolled in a clinical study, designed to collect better data around the safety and effectiveness of a therapeutic (Box 1). CED provides a middle ground between coverage and no coverage and helps reconcile the tension between uncertainty around safety and effectiveness and access to innovative technologies. In addition, CED ensures that the study design addresses the research questions and evidentiary needs of payers. One participant from the Centers for Medicare and Medicaid (CMS) mentioned that the perspective around CED is changing in that it has generally been seen as a way to delay access to a new technology, while now it is being viewed as a mechanism to support innovation.

There have been a number of success stories of CED, such as the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMPPRIS) trial initiated in 2006. Centers for Medicare and Medicaid Services (CMS) issued a CED policy allowing coverage for intracranial stenting for Medicare beneficiaries only when they were enrolled in the study, thereby expediting enrollment in the trial. This trial assessed if treatment with Percutaneous Transluminal Angioplasty and Stenting (PTAS) and medical management was superior to medical management alone in the prevention of a second stroke in high-risk patients with symptomatic intracranial stenosis. The results of this study, published in 2011, showed that patients undergoing PTAS have a much higher rate of stroke or death as compared to patients receiving medical management alone. In this case, the study showed that the risks associated with a technology are greater than the benefits.

Although, there are a number of benefits of using CED, there are challenges to its implementation. Some of the barriers include non-specific legal authority of CED by Medicare, issues around the definition of “medical necessity” by private payers, procuring financial support to support the research costs of a clinical study, and lack of a strong research design strategy that adequately answers the research questions.

CED falls under the category of managed-entry schemes that attempt to address key health policy issues pertaining to increasing cost pressure, uncertain effectiveness, and the improvement in the level of patient benefit per dollar spent. These arrangements between payers and manufacturers are used to reduce uncertainty around a technology, for example by requiring enrollment in a clinical study, which is a CED, while other schemes, such as performance-based risk sharing agreements involve establishing an initial price for a technology and renegotiating that price in the future based on additional clinical data collected.
Adaptive Licensing

Adaptive licensing consists of iterative phases of information gathering, followed by review and regulatory actions to align licensing decisions on market access to drugs with emerging information on benefits and harms over the life of a drug in actual use (Box 2). It differs from the prevailing regulatory approval paradigm in existence today which consists of a binary drug licensing decision, i.e., once approved, drugs are generally perceived to be ‘safe and effective’. However, the very nature of the design of the randomized, controlled trials which serve as the basis for these decisions is flawed, since enrollment in these trials is almost always restricted to patients who are selected to be free from concomitant illnesses or conditions which may be treated with one or more medications. This selection leads to the unpredictability of drug performance in the real-world where this is not the case for a significant number of patients who will be treated. In addition, the unrealistic expectation by stakeholders of perpetual product safety based on limited data at a particular time point is not taken into consideration in today’s regulatory paradigm. This may lead to a tension between satisfying the need for comprehensive information on benefits and risks and the timeliness of patient access. Under the current model of drug licensing, it is difficult to have both.

The basic tenet of adaptive licensing is premised on the assumption that knowledge of a particular technology is not binary and evolves over time. As such, these proposals for reform move away from a “one time” licensing approach with a “magic moment” of approval to a licensing process with several smaller steps. Legal access to market would be based on more than one cycle of data gathering followed by regulatory evaluation and action during the lifespan of a product with each cycle designed to improve evidentiary standards for the therapeutic. Precursors to adaptive licensing already exist in a number of forms including Food and Drug Administration’s (FDA) Accelerated Approval and European Medicines Agency’s (EMA) Conditional Marketing Authorization; FDA’s Risk Evaluation and Mitigation Strategy and EMA’s Risk Management Plan; FDA’s Sentinel Initiative and EMA’s Periodic Safety Update Reports; and EMA requirements for Five Year Reviews of new products.

The key factors that need to be taken into consideration under an adaptive licensing framework are that the initial authorization of a therapeutic is generally limited to smaller and higher-risk patient groups, and there are proactive plans in place for demonstrating safety and continued effectiveness after initial authorization, extending treatment to eligible populations, and, reducing progressively the uncertainty around risks and harms.
Adaptive Regulation in Other Industries – What Can We learn?

This session provided an overview of lessons learned from previous examples of adaptive regulation in non-pharmaceutical industries. In cases of “Planned Adaptation after Disaster,” physical systems and policymaking processes are modified in the aftermath of shocks. In cases of “Planned Adaptation based on Routine Observation,” information on policy relevant sources of uncertainty is systematically gathered and then used to revise and update policies.

Examples of reactive responses to disasters followed by longer term reforms are common. For example, the government of the Netherlands responded to the North Sea flood of 1953 by diagnoses and fixing flaws in dikes and flood gates. The government of Japan responded to the Kobe earthquake of 1995 by identifying flaws in seismic building codes and code enforcement. In addition to fixing physical systems like dikes, flood gates and buildings, these governments also tried to improve their policy making systems. Both the Netherlands and Japan now systematically gather information, perform research on sources of uncertainty, and reevaluate standards in light of emerging information. They reacted to disaster with short term fixes for physical systems and with long term explicitly adaptive fixes for policy systems.

Examples of systems of planned adaption based on routine observation and reassessment are less common. The European Union (EU) strategy on Transmissible Spongiform Encephalopathies (EU TSE Roadmap project) is a good case. The EU set up standards to contain BSE, and also established protocols for gathering information and reevaluating containment measures. Through an iterative process of data collection and evaluation, the EU opted to eliminate some initial controls. This is an example of systematic planned adaptation that led to relaxation. In another example, the United States Environmental Protection Agency (EPA) funded research on the health effects of regulated pollutants and then reevaluated air quality standards in the face of new information. In this instance, iterative cycles of research, observation and reassessment resulted in tightening of standards. In a third example, air safety in the United States is regulated by the Federal Aviation Administration while the investigation and analysis of accidents and near misses is handled by the National Transportation Safety Board. This two headed system, with regulatory and investigatory functions split between two agencies, has worked well and contributed to remarkable improvements in air safety.

In summary, these examples of planned adaptation in other industries may provide useful insights for developing adaptive regulatory and reimbursement approaches in pharmaceuticals.

Applying the Framework: Case Studies

To better understand the benefits and challenges associated with integrating regulatory and reimbursement policy tools, two case-studies were discussed to evaluate the enablers and barriers for a linked approach. One was a recently approved drug for the treatment of metastatic melanoma, while the second was a lipid-lowering therapeutic currently in Phase 2 clinical trials.
Vemurafenib (Zelboraf) for Treatment of Metastatic Melanoma

The first case study discussed was vemurafenib, also known as Zelboraf, for treatment of metastatic melanoma. This case study illustrates a flexible approach to drug licensing that was used by the FDA to enable early access to this important new therapy. The discussion focused on how this example differs from a prospective clinical development plan envisioned under adaptive licensing that integrates CED in a complementary manner.

Metastatic melanoma is an aggressive disease that has a poor prognosis. Until recently, the chemotherapeutic agent dacarbazine was the standard of care. Only 10-20 percent of patients responded to treatment, and their median survival was only six to eight months once treatment began. About half of all melanoma patients have a genetic mutation in the gene BRAF (BRAFV600E mutation) that activates cell division. Vemurafenib, is an oral inhibitor of the mutant BRAF protein, and was recently approved for the treatment of metastatic melanoma that is unresponsive to standard therapy.

Due to the dramatic clinical effectiveness of this drug compared to existing therapies as seen in Phase 1 and 2 trials, the FDA worked with the sponsor to modify the design of the Phase 3 trial to provide patients and providers with the earliest possible access to this important new therapeutic. A companion diagnostic was developed in parallel to test for the specific mutation (BRAFV600E), and the trial enrolled only those patients who screened positive. The trial design was modified to include progression-free survival as a co-primary endpoint along with overall survival. Interim statistical analyses showed that vemurafenib was associated with a relative reduction of 63 percent in the risk of death and 74 percent in the risk of tumor progression in comparison to dacarbazine. Therefore, the drug was approved two years earlier as compared to the timeline for approval, if the original clinical development plan had been followed. The full approval came with extensive post-market data collection requirements on both the safety and effectiveness of the drug.

This case study provides a good example of how flexibility within the current regulatory system can be used, in certain circumstances, to provide accelerated access to patients in need. However, the earlier market access of vemurafenib was not a case of adaptive licensing. There was no prospectively planned clinical development plan that incorporated active monitoring/learning with possible access control following the initial authorization. Vemurafenib received a full approval, albeit with post-approval commitments, which may or may not be fulfilled. In addition, no Risk Evaluation and Mitigation Strategies (REMS) plan was implemented at the time of approval, although one could be adopted, if warranted, on the basis of close post-marketing safety surveillance.

Some of the potential reasons why payers might be interested in CED for this therapeutic would be:

- The full approval was based on progression-free survival with a post-marketing commitment for the submission of the results on overall survival. Payers may be interested in identifying subgroups of better or poorer responders.
Additional studies may be helpful to determine effectiveness of the drug for other mutations in the \textit{BRAF} gene.

The approval was for metastatic disease, and that restriction might be helpful for controlling product diffusion to earlier stages where survival benefits may be more modest.

The preliminary findings, including reports of some adverse events as well as the development of resistance to the drug in some patients, raise questions about how it will work in a larger population.

Participants noted that cancer drugs demonstrating these types of dramatic results for survival are generally covered by payers, but are placed on tiers with high co-payments or are approved under a specialty rider. The use of prior authorization (Box 4) is one potential route for CED, as payers could require participation in a study through this mechanism. The representatives from CMS observed that because vemurafenib is an oral drug, it would be covered under Medicare Part D, and Medicare currently has limited ability to apply CED under Part D. Another complicating factor for payers is controlling diffusion for off-label use. Medicare regulates its coverage for off-label use through compendia listings and, since private payers often follow Medicare, they commonly follow those compendia listings. However, there is concern that the compendia listings are not well supported by evidence.

Manufacturers choose to study efficacy in registration trials for metastatic disease as the evidence hurdles are less since the patient population can be tightly controlled and effects on disease can be in a short, relatively small study. There are other reasons including fewer ethical issues with randomization of patients who have unresponsive metastatic disease. One participant suggested a paradigm change in which drug development has initial approval in a population where benefits are likely to be highest.

Overall, vemurafenib provides a good example of a regulatory approval that is feasible within the existing regulatory framework and can provide patients with early access to a life-saving drug, but leaves uncertain the extent and timing of additional data collection and review. Therefore, defining a complete “adaptive licensing” approach that is prospectively planned with multiple phases of data collection, an initial authorization with well-defined requirements for data generation for full authorization, and incorporates the information needs of end-users including payers, is imperative.

\textbf{Lipid Lowering Therapeutic for Treatment of Hypercholesterolemia}

A novel therapeutic is being developed to treat a selected patient group that has high low density lipoprotein cholesterol (LDL-C) levels, is resistant to current LDL-lowering therapies and has a high risk of coronary heart disease. Preclinical studies show that this therapeutic significantly lowers the LDL-C levels in animals that have a particular genotype while early phase clinical trials demonstrate that administration of this drug to hypercholesterolemic subjects effectively reduces the levels of LDL-C independently and also in combination with statins. The high density lipoprotein cholesterol (HDL-C) and triglyceride levels remain unaffected and there are minimal reported adverse events, after single and multiple dosages.
An initial potential adaptive licensing scenario was presented and discussed by the meeting participants. Under this scheme, regulatory agencies would grant initial authorization for use of the therapeutic in a predetermined patient group (as defined by genotype analysis). The therapeutic could then be studied in a larger population, where the patient inclusion criterion is based on phenotypic analysis. The outcome measure includes measurement of LDL-C, as a surrogate endpoint for overall cardiovascular (CV) risk. The studies for full approval would include evaluating the therapeutic in patients with high-risk concomitant diseases, and measuring morbidity and mortality in addition to LDL-C.

Representatives from payer organizations discussed concerns about using LDL-C as a surrogate endpoint for measuring the risk of coronary heart disease. There were also concerns that the initial price would reflect the high value of using this therapeutic in the highest risk population and that payers would continue to pay this price for lower risk populations that have other effective treatment options and might not require this therapeutic.

A discussion between manufacturers, payers and regulators who attended the workshop offered a modified approach, as depicted in Figure 1. In this scenario, the therapeutic obtains staged approval for different indications and the design and outcomes for each study are defined *a priori* by all stakeholders. The y-axis provides a scale for increased levels of evidence while the x-axis measures the patient characteristics, where patients on the far-left have higher unmet needs and are therefore willing to take higher risks. The payers and regulators are more willing to accept higher levels of uncertainty around safety, if the therapeutic helps patients in the highest risk group. They are less likely to accept increased uncertainty for patients who have other treatment options.

The different studies depicted in Figure 1 are described here:

**Study 1.** The first study is designed to test the therapeutic for a targeted indication to be used in the high risk, high burden patient population as determined by genotypic analysis. The study design would include surrogate endpoints such as lowering of LDL-C for regulatory approval. Regulatory approval for this particular indication would be based on acceptance by payers, regulators, patients, and providers of higher levels of uncertainty around benefit-risk estimates of the therapeutic, as there is a high need for this therapeutic and existing therapies are not effective for reducing the LDL levels in this patient group.

**Study 2.** The second study is conducted simultaneously with the first. In this study, the therapeutic is studied in a larger population, i.e., in patients who by their phenotype may have the genetic deficiency and for whom existing therapies are not sufficient for maintaining a normal lipid profile. The evidentiary requirements for this study would be more rigorous and would include changes in LDL-C levels as well as improvement in the quality of life. For example, if the therapeutic reduced or eliminated the need for apheresis (an expensive and lengthy procedure used to remove LDL-C from the bloodstream), quality of life for the patient would be significantly improved, and the therapeutic would be more cost-effective for payers.
**Study 3.** The third study tests the therapeutic in a much broader population with concomitant diseases, for whom it is essential to show survival benefit and, therefore, measure clinical endpoints such as morbidity and mortality. One of the options discussed by payers was that information on clinical endpoints of interest, such as mortality, could be gathered through an observational study in this population, potentially through administrative databases.

CED studies could be planned in parallel, such that payers would reimburse only for the initially authorized indication after the first study is completed and reimburse for the initial price set by a manufacturer. An evaluated progressive payment scheme could work in parallel with the adaptive licensing scheme. This approach would provide full payment for the approved indication while lower reimbursement for broader use of the therapeutic when it is still being studied in other populations. Payment could be modified once the results of other clinical studies are available. This strategy would provide an incentive to the product manufacturer to develop further evidence on effectiveness of the therapeutic in a broader population. This progressive payment model would ideally result in higher payment for therapeutics that prove to be effective, lower payment for the ones that do not work as well, so that additional evidence generation would be necessary to get maximum reimbursement for the therapeutic. Another advantage of this approach would be...
that all decision makers would know earlier if the therapeutic does not work effectively for a particular population.

In summary, this approach shows how adaptive licensing and CED could be integrated in a prospectively planned manner. This also allows phased data collection where the therapeutic is being tested in different subpopulations. Based on the results of a phased data collection approach, regulatory and reimbursement decisions can be modified.

**Developing an Integrated Approach**

This session focused on strategies for aligning design and implementation of adaptive licensing and CED clinical trials. In the adaptive licensing scheme, the number of patients in the pre-licensing randomized controlled trials (RCTs) or other studies might be smaller and initial authorization might be granted earlier with acceptance of higher levels of uncertainty by decision-makers around benefit-risk estimates of a new therapeutic, approved for use in a specific patient population. The initial authorization would be granted under a set of pre-agreed conditions that require active surveillance and additional RCTs to generate further evidence of safety and effectiveness of the therapeutic in the same or other patient populations. Once a therapeutic receives initial authorization, payers can introduce CED where the therapeutic is covered only when additional evidence can be generated through clinical trials or observational studies. It is also possible to have multiple CED studies for a particular therapeutic to test the safety and real world effectiveness in different populations, with different outcomes and design characteristics depending on the phase of clinical development. The strategy should be designed *a priori* taking into consideration the information needs of payers and regulators during the early phases of product development.

**Criteria for Therapeutic Selection:** It is unlikely that all therapeutics will be appropriate for an aligned CED-adaptive licensing approach. Some of the criteria discussed by the participants included that the therapeutic should address a compelling unmet medical need and have a large impact on costs. In addition, an integrated approach will likely have different economic implications for manufacturers when applied to different therapeutic areas and drug classes. These considerations will be important in determining when an industry sponsor is likely to choose to propose an adaptive licensing/CED approach to regulators and payers.
Box 3: Facilitators of an Aligned CED/Adaptive Licensing Strategy in the United States

CMS-FDA Parallel Review. The Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid (CMS) have initiated a pilot program for concurrent review of FDA premarket review submissions and CMS national coverage decisions for medical devices. The goal of this program is to reduce the interval between FDA approval and medical coverage to enable rapid introduction of innovative products to patients. This approach could also be extended for review of drugs and other medical technologies. Initially, this approach aims to reduce the time between regulatory approval and coverage, and later have mechanisms for sharing the clinical data and evidentiary needs of FDA and CMS.

CMS Solicitation for Public Input on CED. CMS is seeking public input on ways to revise their guidance document that matures CED and better aligns it with the changes in the healthcare system. Public comments are open through early January 2012 and provide a mechanism for aligning CED with adaptive licensing.

The Patient-Centered Outcomes Research Institute (PCORI). PCORI was created to conduct research and provide information on the best available evidence to help patients and their healthcare providers gain a better understanding of the treatment and prevention options available to make more informed treatment decisions. The research funded by PCORI aims to improve the scientific knowledge around the benefits and risks of medical technologies. PCORI research grants could be a source for funding some studies that use an integrated AL-CED approach for further evidence generation on safety and effectiveness.

Study Design: Alignment between the information needs of regulators, payers, and product developers on acceptable study designs that incorporate the evidence needs at each phase of product development is essential for successful implementation of an integrated approach. The key issues pertaining to study design for successful implementation of an aligned strategy include:

- **Acceptance of Greater Uncertainty at Initial Product Authorization:** In some cases, the initial authorization phase will begin with a greater degree of uncertainty about product efficacy and safety than is the norm within the current regulatory paradigm. This will require that a higher risk tolerance be accepted by the target patient population immediately following the initial authorization. The tradeoff for this increased uncertainty is earlier access for patients to important new treatments and the promise of knowledge that is generated from the treatment experience of the target patient population which receives the product under closely mandated and supervised real world conditions.

- **Phased Data Collection Strategy:** This approach requires managed evolution of the product with multiple phases of data collection. Adoption of this approach requires acceptance from all parties that initial authorization comes with a commitment to gather additional data and the therapeutic can be removed from the market or coverage withdrawn if continued investigations are not met.
• **Flexible Research Methods:** Randomization of covered members for an approved therapeutic could be a real issue for health plans and alternate study designs, such as observational studies, should be taken into consideration when designing post-market studies.

• **Study Outcomes:** It may be desirable to delink safety and efficacy studies, studying both safety and effectiveness in later phases of a product’s clinical development cycle.

• **Timeline:** The integrated approach should also clearly define the timeline for initiation and completion of different studies prospectively so that the studies can start in parallel and end in a timely manner.

**Barriers to Implementation and Potential Solutions**

• **Controlled Diffusion of the Therapeutic:** In the current regulatory paradigm, once a product is in the market, off-label use is under the control of the prescribing physician; as a result, payers pay for off-label use of a therapeutic. In an integrated CED-AL approach, initial authorization of a therapeutic may be associated with greater uncertainty, and there should be mechanisms in place to restrict its off-label use. Integrating AL with CED would ensure that there is no access to the therapeutic outside CED studies. A difficult need will be to find prescription controls that allow for monitoring the appropriate use of a therapeutic. Some possible options include registration of distribution channels, such as infusion centers for infused drugs, or the use of prior authorization by health plans (Box 4).

• **Financial Support:** One of the major barriers to conducting CED in the past has been the lack of financial support for conducting clinical studies. Under the aligned approach, industry could pay for the trial and payers cover the cost of the therapeutic, but other sources of funding may be needed. PCORI research grants (Box 3), as noted, above could provide an important source of funds.

• **Post-Market Evidence Development:** One challenge with adaptive licensing is that once a therapeutic gets an initial authorization with post-marketing requirements to collect additional data, in many instances there are no incentives to initiate additional studies. In some cases, studies are initiated but due to lack of enrollment, these are not completed. If payers agree to pay for the therapeutic only in the context of these studies, this may help ensure that studies are initiated and completed in a timely manner.

• **Payer Heterogeneity:** Although, there is generally one market access regulator for a region, there are a large number of payers with considerable heterogeneity in both

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**Box 4: Prior Authorization**

Prior authorization is a requirement that a physician obtains approval from a health plan in order to prescribe a specific medication for a patient. Without this prior authorization, coverage is not provided. Many health plans require prior authorization for very expensive medications. Through this approach, payers have the flexibility in adding criteria such as enrollment in a study or data collection through a registry to support a CED. The key is that a balance needs to be established between access to the drug and the process of prior authorization.
their flexibility to conduct CED and their evidentiary standards for coverage. As an illustration, there are differences between public and private payers, and within private payers, differences between self-insured employers, labor unions, and fully-insured plans that could result in different requirements. It may be beneficial to reach a consensus among the different payers on the evidentiary pathway for a particular therapeutic. This can be achieved by establishing a coordinating organization that can assess the differing needs and align the interests of the different payers.

- One of the issues that may need to be addressed in the future to assure that adaptive licensing is embraced by industry is a modification of the terms of a product’s “patent life” (which may expire before a product’s full market potential is achieved with adaptive licensing) and/or its “regulatory exclusivity life” (the period of time following market entry during which generic competition is excluded).

- A comprehensive adaptive licensing framework is not currently in place in the United States. Barriers around introduction and acceptance of adaptive licensing may include the requirement for changes to existing legislation and/or policies. There may also be political sensitivity to bringing payers into the discussion early on, because of concerns with adding costs and coverage to the discussion that could further delay access to new therapies. Therefore, it might be more expedient to work on an adaptive licensing framework first and then add payers. On the contrary, some expressed concern that adding payers later would delay the development of an integrated framework.

**Conclusions**

Aligning adaptive licensing with CED requires the development of a comprehensive clinical development plan that addresses the data needs of both regulators and payers. This approach allows phased data collection for different indications, and also allows planning studies for evaluating other uses of a therapeutic. It thereby, may minimize “leakage” by restricting the use of the new therapeutic outside a CED study. It also incentivizes pharmaceutical companies to assess alternate uses of the therapeutic, and prospectively plan these studies during early clinical development. Finally, it provides an opportunity to obtain answers to specific research questions that may be different from those needed for regulatory approval.
References


### Appendix 1

#### Participant List

**Industry**

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Payer (Continued)

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### Appendix 2

#### Meeting Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>8:00 AM – 8:30 AM</td>
<td>Check In &amp; Breakfast</td>
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<tr>
<td>8:30 AM – 8:45 AM</td>
<td>Welcome &amp; Introductions</td>
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<tr>
<td>8:45 AM – 9:45 AM</td>
<td><strong>Meeting Overview</strong></td>
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<tr>
<td></td>
<td>• Meeting Purpose &amp; Objectives</td>
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<tr>
<td></td>
<td>• Overview of Coverage with Evidence Development (CED) Overview of Adaptive Licensing (AL) Adaptive Regulation in Other Industries – What can we learn?</td>
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<td>• Conceptual Framework for Linking CED and AL</td>
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<td>9:45 AM – 10:30 AM</td>
<td>Presentation of Case Study:</td>
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<td>• Zelboraf for Metastatic Melanoma</td>
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<td>10:30 AM – 10:45 AM</td>
<td>Break</td>
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<tr>
<td>10:45 AM – 11:30 AM</td>
<td>Presentation of Case Study:</td>
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<td>• Therapeutic for the Treatment of Dyslipidemia</td>
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<tr>
<td>11:30 AM – 12:30 PM</td>
<td><strong>Therapeutic for Treatment of Dyslipidemia: Discussion</strong></td>
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<td>• Design scenarios</td>
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<td></td>
<td>• Applying Adaptive Licensing and Coverage with Evidence Development Strategies</td>
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<tr>
<td>12:30 PM – 1:00 PM</td>
<td>Lunch</td>
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<td>1:00 PM – 2:00 PM</td>
<td>Discussion of Case Studies (Breakout Groups)</td>
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<td>Developing a conceptual framework for linking Adaptive Licensing and Coverage with Evidence Development.</td>
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<td>2:00 PM – 2:30 PM</td>
<td>Breakout Group Reports (10 minutes each)</td>
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<td>2:30 PM – 3:30 PM</td>
<td>Synthesis Discussion</td>
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<tr>
<td>3:30 PM – 4:00 PM</td>
<td>Recommendations for Moving Forward &amp; Adjourn</td>
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