AMCP Academy of Managed Care Pharmacy®

July 13, 2018

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities - Questions and Answers [Docket No. FDA-2016-D-1307]

Dear Sir or Madam:

The Academy of Managed Care Pharmacy (AMCP) thanks the Food and Drug Administration (FDA) for the opportunity to provide comments in response to "*Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers [FDA-2016-D-1307]*" as published in the *Federal Register* on June 13, 2018. AMCP supports the need for timelier and more proactive communications between biopharmaceutical manufacturers and population health decision makers. The need for this proactive communication is especially important now as the United States health care system evolves from a fee-for-service payment system to a modernized system rewarding quality, improved patient outcomes, and value. Therefore, AMCP applauds the FDA for its leadership and recognition of the importance of modernizing the provisions of the Food and Drug Administration Modernization Act (FDAMA) Section 114 as amended by Section 3037 of the *21st Century Cures Act* (Cures) and the creation of a safe harbor for the exchange of preapproval communications. AMCP also appreciates that provisions in the final guidance document align with recommendations issued by AMCP through collaboration with other stakeholders.

AMCP is the nation's leading professional association dedicated to increasing patient access to affordable medicines, improving health outcomes and ensuring the wise use of health care dollars. Through evidence- and value-based strategies and practices, the Academy's 8,000 pharmacists, physicians, nurses and other practitioners manage medication therapies for the 270 million Americans served by health plans, pharmacy benefit management firms, emerging care models and government.

Population health decision makers are organizations and entities that bear financial risk and are responsible for the care of large populations of patients, such as payors, heath care providers, patient advocacy groups, organizations that develop value frameworks, provider sponsored health plans, pharmacy benefit managers, accountable care organizations, and integrated delivery networks. Population health decision makers are extremely sophisticated recipients of health care economic information (HCEI) as they have the education, training, and expertise to critically analyze and evaluate HCEI for credibility and relevance to the patient populations they serve. Enabling communications matters to population health decision makers because they are charged with evaluating the totality of evidence for a particular medication or disease state and then applying that body of evidence to best care for the patients they serve.

In 2016, AMCP first identified the need for better and timelier preapproval and post-approval communications about treatments between biopharmaceutical manufacturers and population health decision makers as a key objective to improving health care decision making. AMCP held two multi-stakeholder Partnership Forums to consider these issues. Participants included a diverse group of stakeholders representing population health decision makers, biopharmaceutical manufacturers, providers, patient advocacy groups, health economists, academia, and others. The multi-stakeholder group at the forums provides the collective credibility to modernize communications between manufacturers and population health decision makers.

These Partnership Forums, *FDAMA Section 114—Improving the Exchange of Health Care Economic Data* held in March 2016 and *Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval* held in September 2016, resulted in consensus recommendations published in AMCP's peer-reviewed journal, the *Journal of Managed Care and Specialty Pharmacy* (JMCP). These consensus recommendations helped inform AMCP's comments and are also described in depth below and included in their entirety in Attachment A and B.

Based on the recommendations from the Partnership Forums, AMCP and its stakeholders offer two consensus recommendations to provide better and timelier communications between biopharmaceutical manufacturers and population health decision makers:

- First, the clarification and responsible expansion of Section 114 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 as amended by Section 3037 of Cures to improve post-approval sharing of HCEI (see Attachment A); and
- Second, the creation of a safe harbor for the exchange of clinical and economic information for emerging therapies prior to FDA approval (see Attachment B).

With the emerging pipeline that offers promising yet potentially expensive therapies that will offer potential cures for certain disease states or the ability to manage conditions on a long-term basis, the need for HCEI is great as the United States health care system begins to consider the overall value of medications and not just cost. Analysis of treatments will require population health decision makers to evaluate research and information beyond clinical trials, including real-world evidence, comparative effectiveness research, and pharmacoeconomic models to determine the value to patient populations. Therefore, AMCP appreciates FDA's timey consideration of these issues and urges FDA to work with stakeholders and Congress to ensure a robust and legally sound process to proactively share this information. AMCP previously submitted comments (Attachment C) to FDA on post-approval and preapproval sharing of HCEI. These comments will focus on preapproval information sharing.

Creation of a Safe Harbor for the Exchange of Clinical and Economic Information for Emerging Therapies Prior to FDA Approval

AMCP is pleased that the final guidance largely aligns with recommendations for preapproval information exchange as described below. AMCP is particularly pleased that the final guidance expands the scope of preapproval communications to include new indications of approved molecules, and not solely new molecular entities. Several imperatives drive the need for communications prior to FDA approval including proper planning, budgeting, and forecasting to accurately account for the impact of new therapies that will enter the market; the successful implementation of value-based payment models; and to account for medications granted breakthrough designation by the FDA that often are approved before clinical trial data is published.

Recommendations from the AMCP Partnership Forum *Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval* include:

- A safe harbor should be established to allow for biopharmaceutical manufacturers to proactively share clinical and economic information about emerging therapies with population health decision makers at

least 12-18 months prior to FDA approval. The establishment of a safe harbor is essential to clearly allow the proactive dissemination of this information and clarify that it is not in violation of the prohibition against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

- Limit exchange to narrow audience: biopharmaceutical manufacturers and population health decision makers only.
- Limit exchange to new molecules and expanded indications with an intent to file only justified by submission of an investigational new drug application; new drug application; supplemental new drug application; or other similar steps.
- PIE should meet the truthful and non-misleading standard and evidence shared should be based on the expertise of professionals in the relevant area and derived using methods that are transparent, disclosed, reproducible, accurate, and valid.
- PIE should be adaptable to include a broad range of information that does not necessarily have to be clinical or scientific evidence, to the extent known and not subject to legal disclosure limitations.
- Exchange of information should be bidirectional and continue until FDA approval.

As noted above, AMCP is pleased that the guidance expanded the scope of the guidance to include new indications for existing molecules Most, if not all, of the factors mentioned in the guidance (product information, indication sought, clinical data, anticipated approval timeline, patient utilization projections, pricing information, targeting/marketing strategies and product related programs or services) are unique to each indication. Anticipating a new indication and properly planning for the impact on budget and expansion of patient populations eligible to receive such medication are vital for payors. Thus to allow payors to prepare for all developments of potential significance to the healthcare market, they need advance information for all new indications, not just for investigational products.

In the types of information that may be communicated as identified by FDA, AMCP also supports the inclusion of data from pivotal phase III clinical trials, patient reported outcomes, pharmacoeconomic data, and other relevant items such as anticipated indications, place of therapy, and routes of administration. Other information that AMCP stakeholders have identified as relevant includes information related to communication related to Drug Enforcement Administration scheduling requirements.

In March 2018, AMCP held a stakeholder workshop to define the characteristics, training and expertise necessary for representatives from biopharmaceutical companies who deliver preapproval and post approval HCEI to payors. The group also discussed suggested timeframes for payors to receive HCEI from manufacturers prior to FDA approval and after the launch of a product. The proceedings from this workshop will be available in the coming months and AMCP will share this information with FDA.

AMCP Continues to Support the Passage of H.R**. 2026 –** ***The Pharmaceutical Information Exchange (PIE) Act of 2018*** **to Create a Legal Safe Harbor for Preapproval Information Exchange**

AMCP urges FDA to work collaboratively with stakeholders and Congress to create a legislative safe harbor for preapproval information exchange by supporting the passage of H.R. 2026 – The Pharmaceutical Information Exchange (PIE) Act of 2018. While AMCP was pleased to see that the FDA guidance allows the proactive communication of certain information by biopharmaceutical manufacturers to payors prior to FDA approval, many stakeholders would be more inclined to engage in this communication under a guidance that is underpinned by a clear and unambiguous statute. Therefore, AMCP encourages the FDA to work with stakeholders and Congress to create a legislative safe harbor for preapproval information exchange so that it is clear that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

In summary, AMCP believes that enabling communications between biopharmaceutical manufacturers and population health decision makers, both pre and post-FDA approval, will help to shift the United States health care system to a focus on value and promote good outcomes for patients. Thank you for the opportunity to provide feedback and for your consideration of our comments. We encourage the FDA to use our organization as a resource as it continues this work.

Sincerely,

Susan A. Cantrell. RPh, CAE
Chief Executive Officer

Attachments:

- Attachment A: AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data. Journal of Managed Care & Specialty Pharmacy 2016 22:7, 826-831
- Attachment B: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval. Journal of Managed Care & Specialty Pharmacy 2017 23:1, 105-112
- Attachment C: AMCP Comments to FDA on draft guidance *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers [FDA-2016-D-1307]*. April 19, 2017.

AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data

SUMMARY

The Food and Drug Administration Modernization Act (FDAMA) of 1997 included Section 114 as a regulatory safe harbor with the goal of increasing the dissemination of health care economic information (HCEI) to those responsible for formulary decision making. HCEI is typically not included within FDA-approved labeling. Although it has been nearly 20 years since passage and enactment of Section 114, proactive distribution of HCEI has been underutilized by biopharmaceutical companies partly because of (a) vague wording in the statute and (b) the absence of FDA-implementing regulations. Consequently, companies and health care decisions makers have had to speculate about the scope of the provisions. As a result, the biopharmaceutical industry has significant concerns about stepping over the line when using the safe harbor. Also, payers and other "payer-like" decision makers (e.g., self-funded corporate insurers) who are trying to make appropriate coverage and utilization decisions are demanding this information but are not receiving it because of the uncertainties in the statute.

Considering this renewed interest by multiple stakeholders regarding the need for revisions and/or guidance pertaining to Section 114, the Academy of Managed Care Pharmacy held a partnership forum on March 1-2, 2016, with a diverse group of health care stakeholders to provide the FDA with considerations for disseminating a guidance document on current thinking for the sharing of HCEI with health care decision makers. Forum participants represented the managed care industry, biopharmaceutical industry, health care providers, pharmacoeconomic experts, policy experts, and patient advocacy groups with specific expertise in the development, use, and dissemination of HCEI. The multistakeholder group represented the key professionals and entities affected by the provisions of Section 114 and present the collective credibility necessary for Congress and the FDA to modernize and operationalize the safe harbor by using the consensus recommendations developed during the forum.

Speakers, panelists, and attendees focused on 4 terms in Section 114 that remain open to interpretation by companies and enforcement bodies: (1) the scope of HCEI, (2) the scope of "formulary committee or similar entity," (3) the definition of "competent and reliable scientific evidence (CRSE)," and (4) the parameters of how information "directly relates to an approved indication." Based on the forum results, it was recommended that the safe harbor for companies' proactive dissemination of information under Section 114 should include health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations. Recommendations also suggested expansion to organizations that evaluate HCEI or develop value frameworks and compendia and individuals in such organizations. Forum participants also recommended that HCEI be truthful, and not misleading, and be based on the expertise of professionals in the relevant area. HCEI must also be developed and disclosed in a transparent, reproducible, and accurate manner.

Forum participants also discussed and agreed on the types of information, format, and processes by which managed care pharmacy and other health care decision makers seek to receive HCEI from biopharmaceutical companies. Finally, participants encouraged the FDA, Congress, and other stakeholders to find ways to ensure that patients or their representative organizations have appropriate access to a full range of information about their medications and that information related to the medication pipeline is communicated to appropriate stakeholders in a timely manner.

J Manag Care Spec Pharm. 2016;22(7):826-31

Health care economic information (HCEI) has long been valued by managed care organizations, payers, pharmacy benefit managers, and other entities that are responsible for drug formulary decision making for its assistance in evaluating the benefits and costs of drugs and health technologies.[1] Nearly 20 years ago, Section 114 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 was instituted to authorize the communication of HCEI between biopharmaceutical companies and formulary committees or similar entities.[2] However, the U.S. Food and Drug Administration (FDA) has yet to release guidance or regulations to provide clarification on this topic; therefore, confusion remains regarding what is permissible under Section 114, leaving interpretation of the statutory language unclear to individual companies and enforcement bodies.

Despite enactment of the law in 1997, proactive distribution of HCEI remains underutilized in large part because of biopharmaceutical companies' concerns that, given the absence of FDA regulations or guidance to clarify the boundaries of the safe harbor, providing economic analysis could result in FDA sanctions for off-label dissemination of information.[1] As biopharmaceuticals become increasingly complex and personalized, and the U.S. health care system becomes increasingly focused on value and quality versus quantity, health care decision makers' evaluation of HCEI for these products is now more important than ever. For these reasons and others discussed in these proceedings, clarification and modernization of Section 114 and/or other laws regarding medical, scientific, and pharmacoeconomic information sharing is necessary to facilitate the communication of evidence for drugs and other health technologies.

Purpose and Discussion Points

To address the clarification and modernization of Section 114, the Academy of Managed Care Pharmacy (AMCP) held a partnership forum on March 1-2, 2016, with a diverse group of health care stakeholders to provide the FDA with considerations for disseminating a guidance document on current thinking for the sharing of HCEI with health care decision makers.

The purpose of the forum was as follows:

1. Provide recommendations to the FDA (to the extent that the forum recommends expansion or change to the statutory safe harbor, then recommendations would be shared with the relevant congressional authorizing committees) for the promulgation of regulations or guidance to provide clarification and consistency of Section 114 requirements:
   - Create definitions for the following terms referenced in Section 114 to clarify what is considered relevant HCEI:
     a. Competent and reliable scientific evidence (CRSE).
     b. Formulary committee or other similar entity.
     c. HCEI.
     d. Directly relates to an approved indication.
   - Articulate the type of information, format, and process by which health care decision makers would like to receive HCEI from biopharmaceutical companies.
2. Consider whether Section 114, or other areas of existing laws and regulations, should be expanded to provide HCEI to additional entities and articulate the value that would be gained. Audiences for consideration include payers, health care providers, accountable care organizations (ACOs), integrated delivery networks (IDNs), patient advocacy groups (PAGs), organizations that develop value frameworks (e.g., American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN], and Institute for Clinical and Economic Review [ICER]), and research societies (e.g., International Society for Pharmacoeconomics and Outcomes Research [ISPOR] and National Pharmaceutical Council [NPC]).

Past, Present, and Future of FDAMA Section 114

Speaker Peter Neumann, director of the Center for the Evaluation of Value and Risk in Health at Tufts Medical Center, opened the forum by providing an overview of the past, present, and future of Section 114. Government regulatory discussions of pharmaceutical promotion and health economic analyses by biopharmaceutical companies began in 1995. This time period also marked the rise of the field of pharmacoeconomics and outcomes research. Organizations that provide and house these types of analyses did not exist at this time. ISPOR, the organization now recognized for advancing the methods of pharmacoeconomics and outcomes research, was just coming into existence. Biopharmaceutical companies began examining what types of drug and health technology information could be actively promoted and in what manner. FDAMA included Section 114 to specify the conditions under which biopharmaceutical companies could promote HCEI.

Although it has been rumored for several years that the FDA would release guidance on Section 114, it has yet to do so.[1] As the interest of managed care organizations, biopharmaceutical companies, and other entities in determining the value of health care interventions by using real-world evidence and comparative effectiveness research continues to increase, the need for clarity is now more important than ever.[3] Many of the terms in Section 114 are not clearly defined in statute or regulations, including the scope of HCEI, the scope of "formulary committee or similar entity," the definition of "competent and reliable scientific evidence," and information included in the term "directly relates to an approved indication." Neumann and Saret (2015) developed hypothetical case studies of 10 categories of HCEI promotions to explore the potential legal and policy implications. These 10 categories included "(1) costing out on-label clinical end points; (2) promotion of a costing exercise to physicians working in an ACO setting; (3) burden-of-illness claims; (4) economic analysis of a formulary restriction policy; (5) extrapolations to doses, populations, or settings not covered in trials; (6) adherence claims; (7) 'utilization of care' as a secondary end point in randomized clinical trials; (8) costing out a competitor drug's adverse event; (9) economic analysis of comparative effectiveness claims using an indirect treatment comparison; and (10) extrapolating from surrogate to long-term outcomes in an economic model," all of which are prime examples of communications sought in the real world.[4]

Moving forward, managed care organizations, biopharmaceutical companies, and other entities are still seeking guidance documents or regulations from the FDA on Section 114. There is a high demand for broader interpretations of Section 114, formal guidance, and regulations, since multiple entities have the need for HCEI in formulary decision making. Additionally, the 21st Century Cures Act (H.R. 6),[5] a bill intended to encourage medical innovation that passed the U.S. House of Representatives in July 2015, contains language that would expand Section 114. A few of these provisions include the following: (1) defining "health care economic information" to acknowledge that all HCEI contains clinical information and allowing companies flexibility around clinical and economic endpoints; (2) disclosure to allow for more transparency of health economic methodology including the analysis and inputs; (3) broadened language to specifically include payers, to suggest that HCEI is not only useful for formulary committees; and (4) "directly relates" was changed to "relates" to suggest that such extrapolations mentioned previously are allowed. Although the 21st Century Cures Act provides more clarity on HCEI, as the U.S. Senate considers similar legislation, it is not certain whether it will contain the language from the House bill. Further, forum participants agreed that while the 21st Century Cures Act was a step in the right direction, it did not provide the level of clarity needed to truly operationalize Section 114, absent guidance or regulations from the FDA. Therefore, it is essential that the FDA avoid any further delays in providing guidance on Section 114.

Current Challenges and Barriers

Currently, significant uncertainties regarding many of the terms stated in Section 114 exist. Challenges and barriers outlined by forum panelists and participants include the following:

- What is the scope of HCEI that can be communicated? One main issue that arises with this statement is that health care economic analyses often contain clinical content, at least at the foundation; therefore, HCEI is not purely an economic claim.
- To whom does "formulary committee or similar entity" refer? Today, health care decision makers include entities that did not exist in 1997, including ACOs and IDNs. "Similar entity" seems to suggest all organizations involved in population health decisions, but this was never specified. Where is the line drawn?
- What constitutes CRSE and how does it differ from the traditional FDA evidentiary "substantial evidence" standard? Section 114 did not specifically define the evidentiary requirements for CRSE, although it is clear that this is a different standard than the "adequate and well-controlled" standard for inclusion of clinical trial information in the FDA-approved labeling. These requirements may include transparency of methodology through "good research practices" (defined by professional societies' guidelines for conducting research) and disclaimers about research and methods, among others. Although professional societies have developed research guideline reports that provide consensus on good research practices, there are many guideline reports from several different professional societies (e.g., ISPOR and AMCP) with guidelines that are not always consistent across reports.
- Does "directly relates" include modeling and extrapolating from intermediate to long-term endpoints or to other subgroups and doses? "Directly relates" seems to suggest that FDAMA 114 is not a vehicle to make HCEI claims beyond the approved indication and the populations or doses in clinical trials.

Given the significant gray areas in Section 114, the evolution of health care since 1997, and the growing need for HCEI by decision makers, clarifying guidance from the FDA is necessary.

HCEI Under FDAMA Section 114

In considering HCEI under Section 114, speakers and panelists discussed how evidence needs have changed since 1997, what constitutes HCEI, how it should be evaluated, and how it is used today. Since 1997, a greater variety of drug and health technologies, at a wider range of prices, have become available. Participants agreed to the following:

- Evidence should be used and shared to provide clarity regarding the value of drugs and other health technologies.
- HCEI includes much more than costs and refers to a broad set of information well beyond the classic randomized controlled trial with limited endpoints and small sample sizes. HCEI includes health care utilization (e.g., hospitalizations and emergency department visits), patient benefits, adherence, endpoint extrapolations, quality of life, and adverse events, in addition to their associated costs.
- Methodology, inputs, and limitations should be transparent. When data are not available and modeling techniques are used, it should be communicated that these models may be used when data are not available but may be updated as information becomes available.
- Evaluation and review are necessary to ensure that scientific evidence is "competent and reliable." Some panelists and speakers suggested that an independent objective body should be responsible for developing consensus recommendations regarding what is considered "good research practice" for CRSE and updating those recommendations on a regular basis as new types of methods and analyses become available. Also mentioned was that HCEI should be evaluated and be made available for formulary decisions.

Suggested Definitions and Rationale for FDA Guidance and Regulation on Terms Used in the Existing Statutory Language of FDAMA Section 114

"Competent and Reliable Scientific Evidence"

Forum participants defined CRSE as "truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on the expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate, and valid."

Rationale:

- The Federal Trade Commission's definition was used as a basis for the Section 114 definition,[9] although there was considerable debate around removing "generally accepted" because it may inhibit the development and use of new studies or data collection methods. As long as innovative methods are transparent, disclosed, reproducible, accurate, and valid, some forum participants noted that CRSE would not need to be "generally accepted."
- "Truthful and non-misleading" was included to reiterate that evidence must be transparent. Although scientific evidence may be competent and reliable, there is still potential for it not to be truthful and to be misleading. In addition, given the constitutional protection for "truthful and non-misleading" communication, this standard should form the basis for permissible information sharing.
- Transparency and disclosure would be met by presenting a full report of the evidence, including the methods, population, and analytic plans, that would be available to decision makers. Additionally, some participants noted that decision makers sometimes request that models be left with them to download, audit, and test, to the extent that this is possible given existing federal fraud and abuse laws.

- The term "reproducible" was a highly debated topic. Panelists and participants noted that a model's results may not be reproducible and including this term may inhibit the use of models. Others debated that the methods should be reproducible, but the results would not be because different data sources (inputs) likely produce different results.
- It was recommended by forum participants that an independent objective entity would be responsible for developing consensus recommendations regarding "good research practices," but this entity would not necessarily be responsible for vetting all HCEI to determine if it is CRSE. However, this independent objective body could be made available to vet HCEI as CRSE should manufacturers need guidance on whether their HCEI meet the standard for CRSE. This entity would consist of a multistakeholder collaborative of representatives from organizations such as AMCP, ISPOR, and NPC, which would conform to requirements under the Federal Advisory Committee Act (FACA).[10]

"Formulary or Other Similar Entity"

Panelists and participants defined "other similar entity" as "health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."

Rationale:

- Examples of "other similar entity" include payers, ACOs, IDNs, and actuaries; pharmacy and therapeutic committees; physician practices involved in risk-sharing arrangements; and organizations that develop compendia, pathways, and/or value frameworks. Flexibility should exist to identify additional entities in the future as the health care environment continues to evolve and as new test models are developed and implemented, such as by the Centers for Medicare and Medicaid Innovation (CMMI).
- Participants debated the option of allowing "no limitations" on the definition of "similar entities" under Section 114, other than that this particular provision would exclude dissemination directly to consumers. Many participants and speakers emphasized that Section 114 is designed to affect decisions related to health care decision making for entities involved in population health and not in direct patient care; therefore, discussion on clarifications should be similarly limited.
- Participants debated whether PAGs should be included as an "other similar entity." Participants in favor of this option suggested that extremely sophisticated PAGs exist and can understand and interpret these data, as well as break the data down to a "patient level." Those not in favor defended the position that there is a potential for abuse as a promotional activity to consumers, and again, that this part of the statute describes the delivery of information designed to affect decisions on population health. Including PAGs as an "other similar entity" is discussed in greater detail later in this report (see the "Recommendations to Congress" section).

"Health Care Economic Information"

Panelists and participants defined HCEI as "any analysis that identifies, measures, or compares the economic, clinical, or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."

Rationale:

- Examples of HCEI include comparative effectiveness research and real-world evidence data. Evidence is presented as a resource used to inform a decision but is not necessarily limited to economic information and includes health care utilization and/or costs.
- Comparative studies should be included under Section 114 as long as the comparator is the standard of care, which may or may not be on-label.
- Unbranded evidence, such as burden of illness claims, needs to be addressed, but perhaps in other laws/regulations, since real-world drug utilization consists of on- and off-label treatments.

"Directly Relates to an Indication Approved"

Panelists and participants defined "directly relates to an indication approved" as "information about a product that may vary from the parameters utilized in a randomized control trial, such as dosage forms, settings, or populations studied," as long as it is still used within the approved disease indication.

Rationale:

- Participants stated that "directly relates" refers to the indication section of the label but does not limit to expanding the population, dosage, or settings within the indication.
- Participants debated the interpretation of "directly" in "directly relates" within Section 114. Some argued that "directly" limits the inclusion of several key attributes of any economic analysis, such as long-term consequences and benefits. Others suggested that Section 114 should be used as a vehicle to describe the real-world use of drugs or therapeutic technologies in individuals only within an approved indication.
- Payers indicated the need for HCEI on pipeline products prior to FDA approval in order to build this information into forecasting and premiums.

Format and Process by Which Managed Care Pharmacy Should Receive HCEI from Biopharmaceutical Companies

Format

Forum participants discussed a format and process by which HCEI could be communicated between managed care organizations and biopharmaceutical companies. Participants discussed using AMCP as a means for housing HCEI. Some participants found AMCP's current dossiers to be an organized and comprehensive resource; however, other participants had little experience with the AMCP dossier process. Therefore, it was noted that this was one approach and one format, but other options exist. As mentioned previously, participants discussed

the possibility of "leave-behind models" that would allow the health care decision maker or entity to download, audit, and test the models. This could also allow for decision makers to modify the assumptions of the model based on their perspectives and their covered populations. Health economic analyses would also be fully disclosed, meaning that bibliography, supporting documents, limitations, and potential biases would be fully detailed. Participants also suggested that leave-behind models might require a safe harbor to provide protection from allegations under the federal anti-kickback statutes associated with the potential that the leave-behind models are of value and could be viewed as potentially inappropriate inducements or incentives to the entity receiving the model.[8]

Process

Taking into consideration all definitions and the format outlined previously, many forum participants encouraged the institution of an objective independent body that would be responsible for developing "good research practice" guidelines for CRSE. Furthermore, participants suggested that a central repository could be implemented once HCEI became available. An alert system could notify covered parties when information is available in the repository to allow people to find promotional material of interest.

Recommendations to Congress to Amend, Provide Clarification, and/or Incorporate Possible Expansion of FDAMA Section 114 or Other Areas of Existing Laws

In addition to the definitions previously outlined, forum participants agreed that "directly relates" should be amended to "relates" under Section 114. "Relates" can also mean a drug or other health technology indication that is not specifically stated in the label. Claims regarding intended indications versus approved indications would have to be specifically addressed by the FDA to provide clarity on what is permissible under this part of Section 114. Furthermore, participants agreed that other amendments to Section 114 would include disclosures of transparency, expansion of additional entities under "other similar entity," and the agreed-upon format and process previously mentioned.

Furthermore, throughout the forum discussion it was discussed that there is need for the FDA and Congress to work together in finding a solution for possibly providing HCEI in 2 additional circumstances. First, because patients increasingly have an economic interest in the value of treatment decisions, there is a need for patients to be able to learn about HCEI in order to be an advocate for their own health care decisions. However, forum participants were cautious to recommend that this type of information be disseminated directly to consumers and debated the appropriate mechanism of making this information available to consumers, such as providing only to PAGs with a certain level of scientific expertise. While no consensus was reached, it was agreed that this area needs to be explored further and that appropriate patient protections would need to be addressed. Second, payers and other entities seek HCEI related to drugs and health care technologies in the pipeline 12-18 months before drug or technology approval. Early dissemination of HCEI would allow payers to build this information into forecasting and premiums, since waiting until approval is often too late. It was agreed that these are important areas of possible expansion for safe harbor, but it may not be within the spirit or original intent of Section 114. Therefore, further discussions in this area as to how other laws or regulations, such as expanding scientific exchange provisions, could be amended to provide this type of access to HCEI for PAGs and pipeline medications are warranted.

Value of Expanding FDAMA Section 114

Revisions or guidance to Section 114 are now more important than ever. Value is increasingly a critical element outlined by private payers and health and human services alike. As biopharmaceuticals become increasingly complex and personalized, and the U.S. health care system becomes increasingly focused on value, it is essential that product value is accurately measured through health economic analyses. Expanding Section 114 would also modernize the statute to align with today's health care system, which now includes a variety of entities, data sources, innovative models, and analytics that did not exist in 1997. Furthermore, expanding Section 114 as previously outlined would allow for better decision making in a collaborative spirit between patients, providers, payers, and other entities.

Information exchange across channels would facilitate a dialogue on the value of a product and further engage more in-depth scientific exchange to address more accurate pharmacoeconomic evaluations. Furthermore, improved dissemination of HCEI to decision makers would drive higher value health care. In its current state, FDAMA Section 114 is too limiting and does not have these intended effects.

Conclusions

Guidance has long been sought by managed care organizations, payers, and drug formulary decision-making entities on FDAMA Section 114. The communication of HCEI is now more important than ever because the products available to treat conditions; available information sources; analytic processes; and the organization, delivery, and reimbursement of health care have vastly evolved in the past few decades. Therefore, now is the time for laws and regulations, even outside of Section 114, to evolve in parallel. The recommendations from this forum's participants to the FDA and Congress to amend, provide clarification to, or expand Section 114 will allow for better decision making in a collaborative environment and ensure appropriate regulatory governance of truthful and nonmisleading HCEI, without interfering with drug and health technology innovation.

Forum Participants

YANJUN (CAROL) BAO, PhD, Senior Director, HCV, Health Economics and Outcomes Research, AbbVie; CHRISTOPHER MICHAEL BLANCHETTE, PhD, MBA, Vice President, Evidence Strategy and Generation, Precision Health Economics (panelist); LAURIE BURKE, RPh, MPH, Founder, Lora Group (panelist); LISA CASHMAN, PharmD, Director Clinical Formulary, MedImpact Health Care Systems (panelist); ELIZABETH J. COBBS, PhD, Executive Director, Center for Observational & Real World Evidence, Merck & Co.; GREGORY DANIEL, PhD, MPH, RPh, Deputy Director, Duke-Margolis Center for Health Policy (panelist); DAN DANIELSON, MS, RPh, Pharmacy Manager, Clinical Services, Premera Blue Cross (panelist); JEFFREY K. FRANCER, JD, MPP, Vice President and Senior Counsel, Pharmaceutical Research and Manufacturers of America (panelist); JENNIFER GRAFF, PharmD, Vice President, National Pharmaceutical Council (panelist); JOEL W. HAY, PhD, MS, MPhil, Professor, University of Southern California (panelist); J. RUSSELL HOVERMAN, MD, PhD, Vice President of Quality Programs, Texas Oncology, Medical Director, The U.S. Oncology Network (panelist); JAY JACKSON, PharmD, MPH, Vice President, Global Health Economics & Outcomes Research, Xcenda; DANIEL C. MALONE, RPh, PhD, FAMCP, Professor, University of Arizona (panelist); JAMES K. MARTTILA, PharmD, MBA, Director, Pharmaceutical Contracting and Formulary Management, Mayo Clinic (panelist); CRAIG MATTSON, MS, MBA, RPh, Senior Director, Formulary Development, Prime Therapeutics; JOAN MCCLURE, MS, Senior Vice President of Clinical Information and Publications, National Comprehensive Cancer Network (panelist); JAY MCKNIGHT, PharmD, BCPS, Director, Clinical Strategies and Formulary Management, Humana (panelist); PHILIP NAUGHTEN, PharmD, Senior Director U.S. Research, Takeda Pharmaceuticals U.S.A.; PETER NEUMANN, ScD, Director, Center for the Evaluation of Value and Risk in Health, Tufts Medical Center (speaker); ELEANOR M. PERFETTO, PhD, MS, Professor, Pharmaceutical Health Services Research, School of Pharmacy, University of Maryland, Senior Vice President, Strategic Initiatives, National Health Council (panelist); CARLY RODRIGUEZ, PharmD, Manager, Clinical Pharmacy Services, OmedaRx; LAURIE WESOLOWICZ, PharmD, Director II, Pharmacy Services Clinical, Blue Cross Blue Shield of Michigan; RHYS WILLIAMS, MSc, DSc, Executive Director, Global Health Economics, Amgen; SUSAN C. WINCKLER, RPh, Esq., Chief Risk Management Officer, Leavitt Partners; LORI ZABLOW-SALLES, Esq., Executive Director, Executive Counsel, Boehringer Ingelheim Pharmaceuticals; and GERGANA ZLATEVA, PhD, Vice President, Payer Insights & Access Lead, Oncology, Pfizer.

AMCP Staff: KEVIN BRUNS, JD, Vice President of Communications & Marketing; SUSAN A. CANTRELL, RPh, CAE, Chief Executive Officer; MARY JO CARDEN, RPh, JD, Vice President of Government & Pharmacy Affairs; CHARLIE DRAGOVICH, BSPharm, Senior Director of Business Development & Strategic Alliances; TERRY RICHARDSON, PharmD, BCACP, Director of Product Development; and SOUMI SAHA, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs.

CORRESPONDENCE: Soumi Saha, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs, Academy of Managed Care Pharmacy, 100 N. Pitt St., Ste. 400, Alexandria, VA 22314. E-mail: ssaha@amcp.org.

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AMCP Partnership Forum: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval

SUMMARY

Current federal laws and FDA regulations have significantly restricted the sharing of clinical and health economic information on biopharmaceuticals that have yet to receive FDA approval. Over the past several years, organizations that make health care coverage decisions, including those that set copayments, premiums, and formulary placement, have expressed a need for receiving this information before approval, as long as appropriate safeguards exist to prevent this information from reaching unintended entities. Population health decision makers have indicated that waiting until FDA approval is often too late for the critical planning, budgeting, and forecasting associated with health benefit design, especially given the recent influx of high-cost medications and scrutiny for better evaluation and preparation. Recognizing that securities laws restrict the disclosure of nonpublic information and may need to be amended, permissible early dissemination would allow population health decision makers to incorporate clinical and economic information for pipeline drugs or expanded indications into financial forecasting for the following year's plan. Access to this information is needed 12-18 months before FDA approval when organizations are deciding on terms of coverage and budgetary assumptions for state health insurance rate filings, Medicare and Medicaid bids, contracts with health care purchasers, and other financial arrangements.

The need for exchange of clinical economic information before FDA approval was first introduced at a previous Academy of Managed Care (AMCP) forum in March 2016, which addressed section 114 of the Food and Drug Administration Modernization Act and the communication of such information after FDA approval. To address preapproval information specifically, AMCP convened a Partnership Forum on September 13-14, 2016. This forum included a diverse group of stakeholders representing managed care, the biopharmaceutical industry, providers, patients, health economists, academia, and others. The multistakeholder group represented the key professionals and entities affected by the federal laws and FDA regulations that restrict the sharing of preapproval information and the collective credibility necessary for proposing this new communication process.

Forum participants primarily focused on 6 items of discussion: (1) creating and defining new terms for how biopharmaceutical manufacturers may provide clinical and economic information 12-18 months before FDA approval; (2) defining the clinical and scientific standards that this information should meet; (3) determining which entities should have access to this information and the value to each; (4) the format and process by which this information should be disseminated; (5) developing definitions for existing terms referenced in current laws, regulations, or guidance documents that would need to be modernized to align with the identified new term; and (6) providing safeguards to prevent this information from reaching unintended entities.

Forum participants selected "preapproval information exchange" (PIE) as the correct term to describe this proposed new communication process and to be inclusive of data from pivotal phase III clinical trials, pharmacoeconomic data, and patient-reported outcomes, as well as other relevant items, including anticipated indications, place in therapy, and routes of administration. Stakeholders agreed that PIE should be truthful, nonmisleading, and include a broad range of information to meet the needs of population health decision makers and health care technology evolution. Recipients of PIE would be limited to population health decision makers who need this information for coverage decisions. The format and process for PIE disseminated should allow for a bidirectional exchange between manufacturers and population health decision makers but should not be proscribed in legislation. Furthermore, new legislative language may be beneficial, since PIE is a novel category of information. New legislation could provide a safe harbor and clarity that PIE does not violate preapproval promotion and the Federal Food, Drug, and Cosmetic Act and its regulations.

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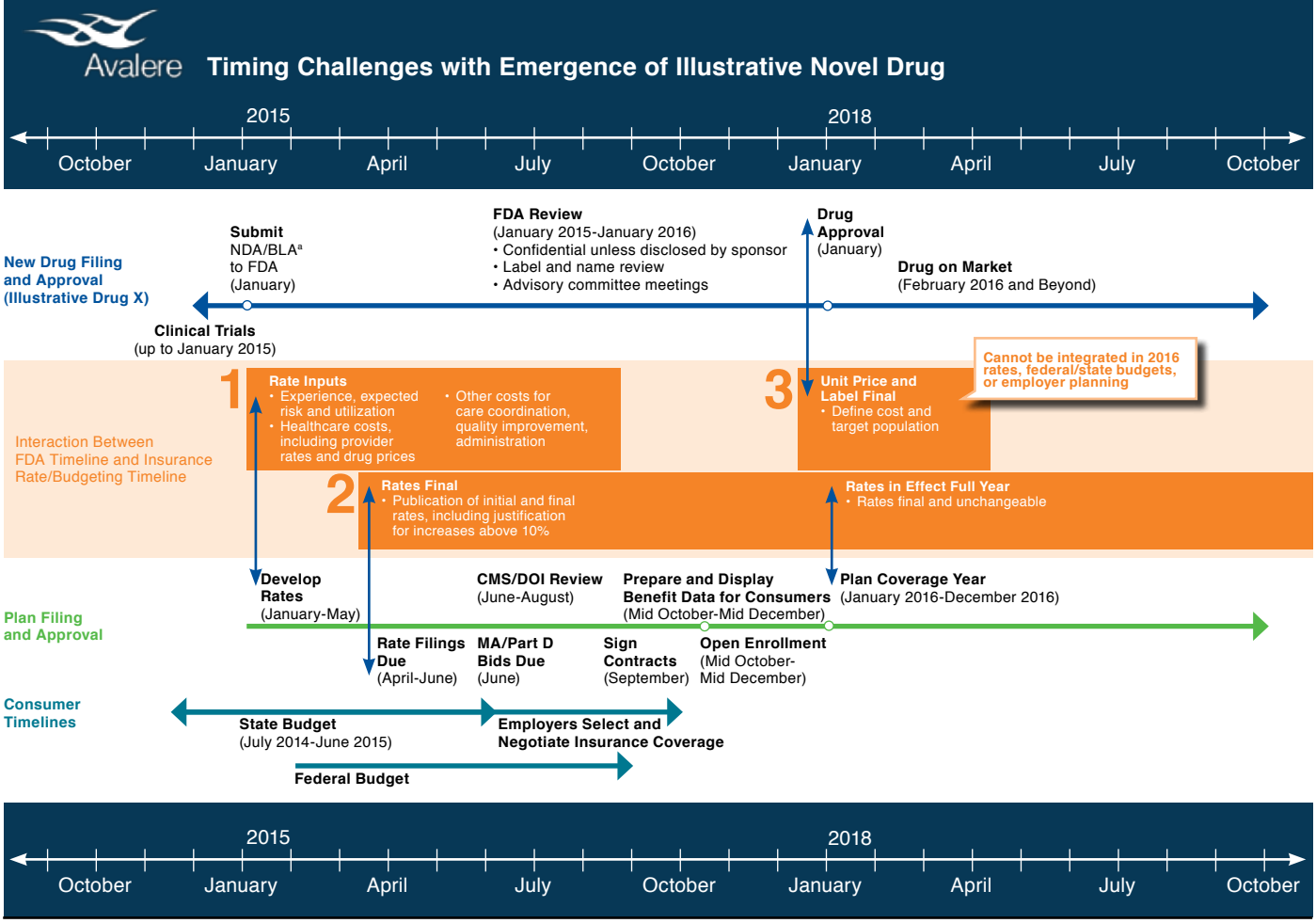
As the U.S. health care system evolves from a historical payment system based on quantity and process to a modernized system rewarding quality and improved patient outcomes, the need for timely communication between biopharmaceutical manufacturers and population health decision makers about emerging therapies is critical for the successful shift to a value-driven system. There are 3 main imperatives driving the need for communications before approval by the U.S. Food and Drug Administration (FDA).[1,2]

First, as a result of new laws such as the Affordable Care Act and state mandates, population health decision makers are required to evaluate their plan designs, formularies, and rates 12-18 months in advance to meet submission deadlines 6-9 months before the beginning of the intended plan year. With rates being filed over a year in advance, proper planning, budgeting, and forecasting are integral for population health decision makers to accurately account for the effect of new therapies that will enter the market. For example, for the 2016 coverage year, population health decision makers analyzed 2014 data in order to submit their 2016 rates by spring 2015 (Figure 1). The budget impact of new therapies that were approved by the FDA after spring 2015 could not be integrated into the 2016 rates. Accurate forecasting and rate setting is critical to ensure that patients have continued access to affordable coverage for their health care needs. Changes are necessary to FDA regulations to expressly permit biopharmaceutical manufacturers to proactively communicate with population health decision makers about emerging therapies before FDA approval so that more accurate forecasting and rate setting are supported, enabling affordable access for all patients to new therapies upon FDA approval.

Second, there is an increased focus on value-based payment models as evidenced by the Medicare Shared Savings Program and a range of initiatives launched and proposed by the Center for Medicare & Medicaid Innovation. Successful implementation of value-based payment models requires understanding the overall value of a therapy, including how pharmacy spending can offset medical costs and vice versa. In addition,

FIGURE 1 Health Insurance Rate Filing and Approval Process



From Eli Lilly and Company and Anthem. Facilitating open communication about emerging therapies. January 29, 2016. Appendix.[2] Reproduced with permission from Eli Lilly and Company.

[a]Median review time 1-2 years.

BLA = Biologic License Application; CMS = Centers for Medicare & Medicaid Services; DOI = Department of Insurance; FDA = U.S. Food and Drug Administration; MA = Medicare Advantage; NDA = New Drug Application.

it requires downstream planning for population health decision makers to change plan design, formularies, and necessary contracts in advance of submitting rates at least a year in advance of the intended coverage year as previously outlined. Therefore, to increase the use of value-based payment models, it is important for biopharmaceutical manufacturers and population health decision makers to be able to share information about emerging therapies before FDA approval in order to provide sufficient time to implement these models in a timely and effective manner upon FDA approval.

Finally, the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) created an expedited approval pathway allowing the FDA to grant priority review if preliminary clinical trials indicate that a therapy may offer substantial treatment advantages over existing options for patients with serious or life-threatening diseases.[3] Under the expedited approval pathway, therapies may be approved by the FDA before clinical trial data are published and made publicly available, thereby making it very difficult for population health decision makers to determine whether a therapy is appropriate for a patient if they receive a coverage request before publication of the data. Guidelines and peer-reviewed compendia sources are even further delayed in providing population health decision makers with reputable reference material for making sound clinical judgements when published clinical data are not available. In these situations, enabling preapproval information

TABLE 1 FDA Guidance and Other Initiatives Regarding Clarification of the Dissemination of Off-Label Drug Information

Year	Topic	Title (if applicable)
1997	Guidance on the scientific exchange of original trial results and off-label information	Industry-Supported Scientific and Educational Activities[4]
2009	Guidance on the distribution of peer-reviewed scientific and medical publications regarding unapproved new uses of approved drugs and approved/cleared medical devices	Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices[5]
2011	Guidance reflecting responses to unsolicited requests	Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices[6]
2011	MIWG petition regarding clarification on off-label communication	Citizen Petition, FDA-2011-P-5012[9]
2013	MIWG petition requesting a constitutional response to 2011 petition (above)	Citizen Petition, FDA-2013-P-1079[10]
2014	Update to 2009 guidance	Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices[7]
2015	Declaration that detailed the FDA's initiatives to accommodate policies to foster stakeholder interests in off-label communication	Declaration by Janet Woodcock[11]

FDA = U.S. Food and Drug Administration; MIWG= Medical Information Working Group.

exchange (PIE) is critical to ensuring that population health decision makers are aware of the information available to date on emerging therapies granted breakthrough designation by the FDA so that they are prepared to make coverage decisions for patients immediately upon FDA approval.

Restricting Information Dissemination

Current federal laws and FDA regulations have significantly restricted communications between biopharmaceutical manufacturers and population health decision makers for emerging therapies before FDA approval, despite clear recognition that budgeting and forecasting by payers is critical to ensure that patients have access to new treatments as soon as possible following market approval. Over the past 3-4 decades, the FDA has disseminated various policy documents addressing this issue.[4-7] While safe harbors for off-label communication already exist, the interpretation is unclear, and enforcement involves various entities with differing approaches (i.e., Health and Human Services Office of the Inspector General, Federal Trade Commission, Department of Justice, and state governments).[8] FDA regulations ensure access to safe and effective medications, while other agencies must ensure prevention of fraud, waste, and abuse, and marketplace competition. Uncertainty regarding safe harbors and the fear of enforcement has limited the dissemination of preapproval information by manufacturers, despite population health decision makers and others expressing a strong need for this information much earlier in the drug development process. There is a definitive need to refine and clarify laws governing activities under the purview of the FDA to help diminish concerns about the possibility of legal action by other agencies. More recently, the FDA has drafted guidance to take steps to support solutions to distinct, yet related, communication challenges; granted petitions to elucidate on this topic; and announced a public hearing to review policies and clarify standards for off-label communication.[4-11] This topic has also been heavily discussed outside of the FDA, including at AMCP's FDAMA Section 114 forum, 21st Century Cures proposals for reform of Section 114, Biotechnology Innovation Organization and Pharmaceutical Research and Manufacturers of America's principles on responsible sharing for truthful and non-misleading information, among others (Table 1).[12-14]

Given these circumstances and others discussed in the following proceedings, further recommendations, guidance, and legislation are needed to provide clarity on the dissemination of information before FDA approval.

Forum Purpose and Discussion Points

To address the long-debated issue of proactive dissemination of clinical and health economic information on products before FDA approval, the Academy of Managed Care Pharmacy (AMCP) held a Partnership Forum on September 13-14, 2016, in Tysons Corner, Virginia, with a diverse group of health care stakeholders to provide recommendations for Congress and the FDA. The purpose of this forum was to discuss the following 6 items:

1. The term that would be used to describe the ability of biopharmaceutical manufacturers to proactively share clinical and economic information about medications in the pipeline with payers and other entities before FDA approval.
2. The standards that clinical and economic information should meet before FDA approval.
3. Stakeholders who should have access to clinical and economic information before FDA approval and the value of this information to each of these entities or individuals.
4. The preferred format and process by which eligible entities would like to receive clinical and economic information from biopharmaceutical manufacturers before FDA approval.
5. The definitions for existing terms referenced in current laws, regulations, or guidance documents (i.e., labeling, misbranded, or intended use) that would need to be modernized to align with the identified new term for the exchange of clinical and economic information before FDA approval.

TABLE 2 Summary of the AMCP FDAMA 114 Partnership Forum[12]

Objective	AMCP convened a Partnership Forum for stakeholders to discuss clarification and possible expansion of FDAMA Section 114 to obtain consensus recommendations on how information related to this statute should be disseminated.	
Key stakeholders	Pharmaceutical industry, managed care industry, health care providers, pharmacoeconomic experts, health policy experts, and patient advocates	
Recommendations: Terms, Definitions, and Key Points		
Term	**Definition**	**Key Points**
Competent and reliable scientific evidence	"Truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on the expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate, and valid."	Models would be left behind with reproducible methods.
Formulary or other similar entity	"Health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."	• "Other entity" needs to be flexible as the health care industry evolves over time. • The role of the individual needs to be a key consideration. • Inclusion of patient advisory groups was debated, since some of these groups are sophisticated and have the ability to interpret this information, but not all do, so proper protections need to be considered.
Health care economic information	"Any analysis that identifies, measures, or compares the economic, clinical, or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."	Includes noneconomic information as well, since clinical and quality life endpoints are a part of economic evaluation.

AMCP=Academy of Managed Care Pharmacy; FDAMA=Food and Drug Administration Modernization Act; HCEI=health care and economic information.

6. The public health protections that should be considered to prevent the dissemination of clinical and economic information to unintended entities before FDA approval.

AMCP previously held a Partnership Forum in March 2016 to address communications of health care economic information (HCEI) after FDA approval. More specifically, the March forum discussed the clarification and possible expansion of Section 114 of the Food and Drug Administration Modernization Act (FDAMA) to obtain consensus recommendations on how information related to this statute should be disseminated.[12] While the recommendations from the March forum (Table 2) were focused on HCEI dissemination after FDA approval, a key recommendation was that further discussion was warranted to create recommendations for information exchange before FDA approval.

Stakeholders participating in the September Partnership Forum on preapproval communications were separated into 3 groups. Throughout the forum, each group, which was composed of representatives from the biopharmaceutical industry, payers, provider organizations, academia, health economists, and patient advocacy groups, among others, began its discussion with the question of whether the recommendations from the March forum on post-FDA approval communications were applicable to pre-FDA approval communications or whether the latter required adjustments given the differences in purpose and use before versus after FDA approval. The following recommendations and discussion points are reported to reflect where there was agreement, and where further discussion is warranted.

Terminology to Describe the Sharing of Preapproval Clinical and Economic Information

When considering the terminology that should be used to describe the ability of biopharmaceutical manufacturers to proactively share clinical and economic information about medications in the pipeline with payers and other entities before FDA approval, debate among the 3 groups focused on 3 areas: (1) the term "preapproval," (2) whether the information to be communicated should be information or evidence, and (3) whether the method of conversation should be deemed an exchange or information sharing.

Preapproval

The groups discussed the need for a term that is narrow enough to be included in legislation or adopted in guidance. Whether to include "preapproval" in this term was debated. Stakeholders reached consensus that the final recommended term should differentiate what type of information is to be shared. Including the word "preapproval" in any such term would highlight that the term refers to information disclosed for forecasting, planning, and budgeting before FDA approval. A key point of discussion was when pricing information would be available for medicines initially entering the market. Some stakeholders noted that pricing may only be known shortly, if not immediately, before product launch, while other stakeholders expressed an interest in receiving pricing information, or at least a range of possible prices, as early as possible. Stakeholders recognized, however, that manufacturers must

comply with securities and trade secrets laws that restrict the dissemination of material nonpublic information, which could include pricing, as well as certain clinical trial data.

Information Versus Evidence

The terms "information" and "evidence" were used to describe the clinical and economic data to be communicated. Although the term "scientific information" was proposed, stakeholders agreed that this term may be misinterpreted as being limited to research studies subject to scientific rigor, when instead, the proposed term should be inclusive of additional purposes (e.g., identifying potential patient-populations, distribution requirements, and budgeting). Some stakeholders indicated that as biopharmaceuticals move through the early phases of development, information builds over time and eventually leads to a body of evidence in the later phases of development and throughout the product life cycle. Furthermore, the term "information" was deemed appropriate by some because "evidence" may be viewed as only the types of data that involve a statistical comparison and may limit the use of models and valuable cost analyses. Stakeholders expressed that models cannot be classified as evidence, since they are simply tools to develop estimations, and there was a strong concern among many stakeholders that deeming a model as evidence would lead to misinterpretation as to what such models can and cannot demonstrate and depict from a level of certainty. Those who supported use of the term "evidence" stated that "information" is a broader and more encompassing term that may not have as much weight in the scientific community. The concept of information versus evidence is discussed in more detail throughout this proceedings document.

Exchange Versus Information Sharing

The third area of discussion focused on the terms "exchange" versus "information sharing." Supporters of the term "exchange" felt that the use of this term would signify bidirectional conversations between decision makers and manufacturers and reinforce an ongoing dialogue between the 2 parties. Proponents of the term "information sharing" thought that the term "exchange" would be confused with scientific exchange, which has traditionally been interpreted to be applicable to investigational new drugs under 21 CFR 312.7(a) and therefore expressed hesitance in using this term.

After thorough discussion, stakeholders agreed on the term "preapproval information exchange" (PIE), which referred to the proactive sharing of clinical and economic information by manufacturers to decision makers (entities are discussed later in the proceedings) at least 12-18 months before FDA approval and the ongoing discussions between the 2 sharing entities as information evolves into evidence throughout drug development. Furthermore, stakeholders agreed that this preapproval communication only applies to those biopharmaceutical manufacturers who intend to file for a new indication (new molecules and new indications), thereby limiting the risk for off-label promotion. Stakeholders agreed that the intent of a biopharmaceutical manufacturer to file would need to be justified by submission of an Investigational New Drug (IND) application, New Drug Application (NDA), Supplemental New Drug Application (sNDA), or other similar steps.

Standards for Preapproval Information

Discussion on the question "What standards should clinical and economic information shared prior to FDA approval meet?" began with the definition of "competent and reliable scientific evidence" as developed in the FDAMA 114 forum (Table 2) and how to differentiate the preapproval setting from the postapproval setting. Overall, stakeholders agreed that the standards for this information should be based on the FDAMA 114 forum definition, with a few proposed exceptions:

- "Information" should be either added to the definition or should replace "evidence."
- A minimum set of standards should be set for this information, but as a biopharmaceutical product approaches approval, the information would become stronger and evolve into evidence.
- It was emphasized that because the information about a product could change and augment over time, any disclosure of information for PIE purposes needed to include transparency regarding the methods and results (all of which would need to be done in a truthful and non-misleading manner) with appropriate disclosures of uncertainty and limitations inherent in such information, and methods would need to be reproducible—not the results).

Some stakeholders expressed that all-inclusive information sharing, with ultimately no restrictions, may allow too much lenience, while being too specific may inhibit manufacturers from sharing important information with population health decision makers that would be of value to their decisions and ultimately be important for planning and forecasting purposes. As mentioned in the previous section, limiting the standards to "evidence" may cause legal concern and be interpreted as requiring a level of research or replicability for all information disclosed, which might be unattainable at certain stages of the product's development, whereas the intent is to be able to include additional items such as anticipated indications, place in therapy, routes of administration, distribution channels, and potential budget impact.

Entities and Individuals Who Should Receive Preapproval Information

During the FDAMA 114 forum, it was decided that entities who should receive HCEI after FDA approval would be "health care decision makers beyond health plan formulary

committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations" (Table 2). Stakeholders were asked to consider these same entities for preapproval purposes, in addition to pharmacy and therapeutic committees, managed care pharmacy, health care providers, accountable care organizations (ACOs), integrated delivery networks, patient advocacy groups (PAG), organizations that develop value frameworks (e.g., American Society of Clinical Oncology and National Comprehensive Cancer Network), organizations that develop clinical practice guidelines (e.g., American College of Cardiology and American Diabetes Association), research societies (e.g., International Society for Pharmacoeconomics and Outcomes Research), actuaries, contract specialists, and others.

All stakeholders agreed that population health decision makers such as managed care organizations and pharmacy benefit managers would be eligible to receive preapproval information. In addition, certain integrated delivery networks (IDNs) and ACOs that bear financial risk for biopharmaceuticals would also be eligible to receive preapproval information. These population health decision makers were included because entities and individuals within these organizations need to receive this information in advance of FDA approval for budgeting, forecasting, and coverage decision purposes.

Forum stakeholders also considered whether other entities that are "influencers," such as groups that develop value frameworks and clinical practice guidelines should be included in PIE. Some stakeholders thought that clinical practice guidelines developers would need to know this information, since the evolution of guidelines is a lengthy process, and it would be beneficial to know this information for the next guideline update. A limited number of stakeholders thought that some benefit exists in expanding this information sharing to PAGs, since the FDA is moving toward more patient-focused drug development. However, the majority of stakeholders strongly argued that the need for HCEI is for entities that have accountability for forecasting costs to ensure patient access and coverage, which is not the case for influencers or PAGs. While preapproval information sharing with influencers and PAGs was considered, there was consensus that the pre-FDA approval information most valuable to influencers and PAGs was clinical in nature, not preliminary economic or financial data. Furthermore, entities such as influencers or PAGs could receive this information through the usual channel of unsolicited requests. Therefore, the majority of stakeholders agreed that only entities who manage a population's health should receive preapproval information.

Preferred Format and Process for Receiving Preapproval Information

After reviewing the recommendations set forth at the FDAMA 114 forum, stakeholders were asked the question "What is the preferred format and process by which eligible entities would like to receive clinical and economic information prior to FDA approval from biopharmaceutical manufacturers?". Overall, stakeholder consensus supported the creation of a flexible means of providing this information that allows for a bidirectional exchange between manufacturers and population health decision makers and that a specific format or process should not be prescribed in legislation. Furthermore, AMCP was identified as a potential driver and leader in this space, given that AMCP has an established process for communication of information about biopharmaceutical products to inform decisions made by formulary committees. This process is currently restricted to unsolicited requests but could be adapted for PIE. Conversely, a few key points were debated:

1. *Central repository versus repositories for each manufacturer.* Some stakeholders thought that having multiple repositories (each for a different biopharmaceutical manufacturer) would simplify the risk of unintended users gaining access to preapproval information. Others stated that having the ability to compare medications and technologies in a central repository during a single log-in would allow for a more simplified, effective process. The central repository would allow for alerts once information is updated—decision makers could choose to opt-in and the frequency of the alerts they would like to receive (e.g., once a month or once a week). Later in the discussion, stakeholders noted that AMCP already has a central repository system in place for dossier submissions and viewing; therefore, this same system could be adapted as an option for communicating information in the preapproval setting.
2. *Standardized format versus flexible format.* An AMCP dossier-light format was initially suggested by many stakeholders, while others were concerned that not all end users, such as IDNs and ACOs, would be as familiar with this format; therefore, the format would need to be adaptable and flexible to suit the needs of organizations or entities. Furthermore, technology is rapidly evolving and developing, so a format developed today may not be useful tomorrow. Others disagreed, stating that a standardized format with the ability to locate the same information in the same location between 2 products would allow for a more simplified, consistent process.
3. *Communication and notification.* Communications via a repository would include notifications to decision makers once information was updated, options for manufacturers to share models and slide-decks, and one-on-one conversations between manufacturers and decision makers. More importantly, manufacturers and decision makers would have the option to choose the type and frequency of

engagement, depending on their individual needs, and whether to use a central repository or another process for exchanging this information.

Stakeholders ultimately agreed that the forum discussion is a starting point for the consideration of format options and that a specific format or process should *not* be prescribed in legislation but should be developed collaboratively between the manufacturers and population health decision makers who would be exchanging this information. The group agreed that given AMCP's history of providing this type of information, it is in a good position to serve as a leader and developer for providing information under PIE.

Definitions for Existing Terms in Current Laws, Regulations, or Guidance Documents

Given the existing terms included in current laws, regulations, and guidance documents, stakeholders were asked the question "How should the definitions for existent terms, referenced in current laws, regulations, or guidance documents (such as labeling, misbranded, or intended use) be modernized to align with the identified new term for the exchange of clinical and economic information before FDA approval?". Stakeholders quickly reached a consensus that PIE would need to have its own safe harbor, in a manner consistent with existing law.

Public Health Protections to Prevent the Dissemination of Preapproval Information

Stakeholders considered the public health protections required to prevent the dissemination of preapproval information and agreed that it should function similarly to the system in place for HCEI under FDAMA Section 114. The stakeholders agreed that certain public health protections are already in place through other legislation, so there may not be a need to create further protections beyond those already enacted.

Conclusions

Currently, the sharing of clinical and health care economic information on new products and indications before FDA approval is significantly restricted by federal laws and FDA regulations regarding product promotion. Population health decision makers have expressed a need for receiving this information at least 12-18 months before FDA approval to properly plan, budget, forecast, and care for the populations they serve, as long as safeguards are in place to prevent preapproval information from reaching unintended entities. The recommendation from this Partnership Forum is for Congress to establish a safe harbor for preapproval information exchange between biopharmaceutical manufactures and population health decision makers to encourage better decision making, without interfering with innovation in the biopharmaceutical and health technology industry.

Forum Participants

ALEXIS AHLSTROM, MPH, Director, GlaxoSmithKline; ANDREW BEHM, PharmD, CGP, Vice President, Express Scripts; CHRISTOPHER MICHAEL BLANCHETTE, PhD, MBA, Vice President, Evidence Strategy & Generation, Precision Health Economics, Associate Professor, Public Health Sciences, University of North Carolina at Charlotte; ELIZABETH L. BRUSIG, PharmD, MBA, Clinical Pharmacy Specialist, Optima Health Plan; SUSMITA CHAVALA, PharmD, MHA, Senior Principle, Clinical Policy, Prime Therapeutics; GREGORY DANIEL, PhD, MPH, RPh, Deputy Director, Duke-Margolis Center for Health Policy; AMY DUHIG, PhD, Senior Director, Outcomes Research, Xcenda; PAUL EITING, MPP, Senior Manager, Value-Based Policy, Blue Cross Blue Shield Association; ELIZABETH ENGELHARDT, RN, BSN, Head of Specialty Strategy & Clinical Management, Aetna; JEFFREY K. FRANCER, JD, MPP, Vice President and Senior Counsel, Pharmaceutical Research and Manufacturers of America; JENNIFER GRAFF, PharmD, Vice President, Comparative Effectiveness Research, National Pharmaceutical Council; JOEL W. HAY, PhD, MS, MPhil, Professor, University of Southern California; DOROTHY HOFFMAN, MPP, Director, Global Public Policy/Head, U.S. Health Policy, Eli Lilly and Company; KAT WOLF KHACHATOURIAN, PharmD, Vice President, Pharmacy Services & Strategy, Qualchoice Health Plan Services; CRYSTAL L. KUNTZ, MPA, Vice President, Policy and Regulatory Affairs, America's Health Insurance Plans (AHIP); JEFF LEE, PharmD, FCCP, Associate Professor, Pharmacy Practice, Lipscomb University College of Pharmacy; ERIN LOPATA, PharmD, Manager of Clinical Pharmacy, UPMC Health Plan; JAMES K. MARTTILA, PharmD, MBA, Director, Pharmaceutical Contracting and Formulary Management, Mayo Clinic; JOAN S. MCCLURE, MS, Senior Vice President of Clinical Information and Publications, National Comprehensive Cancer Network; NEWELL MCELWEE, PharmD, MSPH, Associate Vice President, Center for Observational and Real World Evidence, Merck; COREY PELLETIER, PhD, Director, US Health Economics & Outcomes Research, Celgene; ELEANOR M. PERFETTO, PhD, MS, Professor, Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Senior Vice President, Strategic Initiatives, National Health Council; MICHAEL RYAN, PharmD, Senior Vice President, Value Access & Payment, Bristol-Myers Squibb; SHEILA M. THOMAS, PharmD, Senior Director, Evidence Based Medicine, Sanofi; ROBIN S. TURPIN, PhD, Lead Director, HEOR, Takeda Pharmaceuticals, USA; ANTHONY WANG, PhD, MPH, Senior Manager HEOR, AbbVie; MELEA WARD, PhD, PharmD, BCPS, Director, Outcomes and Evidence, Pfizer Oncology; JAMES WEATHERALL, BBA, MA, PhD, Director, Health Economics & Outcomes Research, Novo Nordisk; SUSAN C. WINCKLER, RPh, Esq., Chief Risk Management Officer, Leavitt Partners; KRISTINA YU-ISENBERG, PhD, MPH, RPh, Vice President and Head, Evidence Generation and Analytics, Intarcia Therapeutics; and LORI ZABLOW-SALLES, Esq., Executive Director, Executive Counsel, Boehringer Ingelheim Pharmaceuticals.

AMCP STAFF: SUSAN A. CANTRELL, RPh, CAE, Chief Executive Officer; MARY JO CARDEN, RPh, JD, Vice President of Government & Pharmacy Affairs; CHARLIE DRAGOVICH, BSPharm, Senior Director of Business Development & Strategic Alliances; ASHLEY LANHAM, PharmD, MBA, Manager of Student Development & New Practitioner Programs; and SOUMI SAHA, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs.

CORRESPONDENCE: Soumi Saha, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs, Academy of Managed Care Pharmacy, 675 N. Washington St., Ste. 220, Alexandria, VA 22314. E-mail: ssaha@amcp.org.

DISCLOSURES

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Academy of Managed Care Pharmacy®

April 19, 2017

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities - Questions and Answers [Docket No. FDA-2016-D-1307]

Dear Sir or Madam:

The Academy of Managed Care Pharmacy (AMCP) thanks the Food and Drug Administration (FDA) for the opportunity to provide comments in response to "*Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers [FDA-2016-D-1307]*" as published in the *Federal Register* on January 19, 2017. AMCP supports the need for timelier and more proactive communications between biopharmaceutical manufacturers and population health decision makers. The need for this proactive communication is especially important now as the United States health care system evolves from a fee-for-service payment system to a modernized system rewarding quality, improved patient outcomes, and value. Therefore, AMCP applauds the FDA for its leadership and recognition of the importance of modernizing the provisions of the Food and Drug Administration Modernization Act (FDAMA) Section 114 as amended by Section 3037 of the *21st Century Cures Act* (Cures) and the creation of a safe harbor for the exchange of preapproval communications.

AMCP is the nation's leading professional association dedicated to increasing patient access to affordable medicines, improving health outcomes and ensuring the wise use of health care dollars. Through evidence- and value-based strategies and practices, the Academy's 8,000 pharmacists, physicians, nurses and other practitioners manage medication therapies for the 270 million Americans served by health plans, pharmacy benefit management firms, emerging care models and government.

Population health decision makers are organizations and entities that bear financial risk and are responsible for the care of large populations of patients, such as payers, provider sponsored health plans, pharmacy benefit managers, accountable care organizations, and integrated delivery networks. Population health decision makers are extremely sophisticated recipients of health care economic information (HCEI) as they have the education,

training, and expertise to critically analyze and evaluate HCEI for credibility and relevance to the patient populations they serve. Enabling communications matters to population health decision makers because they are charged with evaluating the totality of evidence for a particular medication or disease state and then applying that body of evidence to best care for the patients they serve. In the current legal and regulatory framework, population health decision makers are significantly restricted to accessing information based on unsolicited requests only, which is a very cumbersome process that hinders access to comprehensive, accurate, and reliable information about treatments before and after FDA approval. Therefore, population health decision makers need access to better and timelier information from biopharmaceutical manufacturers so they can have access to available HCEI to best care for the patients they serve.

In 2016, AMCP identified the need for better and timelier preapproval and post-approval communications about treatments between biopharmaceutical manufacturers and population health decision makers as a key objective to improving health care decision making. AMCP held two multi-stakeholder Partnership Forums to consider these issues. Participants included a diverse group of stakeholders representing population health decision makers, biopharmaceutical manufacturers, providers, patient advocacy groups, health economists, academia, and others. The multi-stakeholder group at the forums provides the collective credibility to modernize communications between manufacturers and population health decision makers.

These Partnership Forums, *FDAMA Section 114—Improving the Exchange of Health Care Economic Data* held in March 2016 and *Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval* held in September 2016, resulted in consensus recommendations published in AMCP's peer-reviewed journal, the *Journal of Managed Care and Specialty Pharmacy* (JMCP). These consensus recommendations helped inform AMCP's comments and are also described in depth below and included in their entirety in Attachment A and B.

Based on the recommendations from the Partnership Forums, AMCP and its stakeholders offer two consensus recommendations to provide better and timelier communications between biopharmaceutical manufacturers and population health decision makers:

- First, the clarification and responsible expansion of Section 114 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 as amended by Section 3037 of Cures to improve post-approval sharing of HCEI (see Attachment A); and
- Second, the creation of a safe harbor for the exchange of clinical and economic information for emerging therapies prior to FDA approval (see Attachment B).

With the emerging pipeline that offers promising yet potentially expensive therapies that will offer potential cures for certain disease states or the ability to manage conditions on a long-term basis, the need for HCEI is great as the United States health care system begins to consider the overall value of medications and not just cost. Analysis of treatments will require population health decision makers to evaluate research and information beyond clinical trials, including real-world evidence, comparative effectiveness research, and pharmacoeconomic models to determine the value to patient populations. Therefore, AMCP appreciates FDA's timey consideration of these issues and urges FDA to work with stakeholders and Congress to ensure a robust and legally sound process to proactively share this information.

Clarification and Responsible Expansion of FDAMA Section 114 to Improve Post-Approval Sharing of HCEI

FDAMA Section 114 created a safe harbor to allow for the proactive dissemination of HCEI by manufacturers to formulary committees or other similar entities on medications post-FDA approval. Prior to the release of the current draft guidance document, regulations or guidance has never been issued and therefore the safe harbor has been underutilized due to lack of clarity. A recent survey of payors and manufacturers (see Attachment C and D) regarding utilization of FDAMA Section 114 found that over 60% of payors noted a gap between their need for HCEI versus what has been available to them and shared that product decision making would be very much or extremely improved (54%) if the gap between HCEI needed for formulary decision-making and available HCEI were addressed. The survey also found that many manufacturers (41%) found gaining approval of HCEI materials under FDAMA Section 114 to be very or extremely difficult and largely noted that decisions were somewhat (56%), not very (15%), or not at all (7%) consistent across brands. With regard to the changes proposed by the AMCP Partnership Forum to add clarity to FDAMA Section 114, the majority of payors (52% to 66%) and manufacturers (62 to 84%) very much or completely agreed that the suggested changes would be helpful in improving their organization's ability to effectively communicate HCEI.

Recommendations from the AMCP Partnership Forum *FDAMA Section 114—Improving the Exchange of Health Care Economic Data* include:

- Health care economic information (HCEI) should be:
    - Truthful and not misleading, and be based on the expertise of professionals in the relevant area
    - Developed and disclosed in a transparent, reproducible, and accurate manner
    - Expanded to include clinical information
- Eligible recipients of FDAMA Section 114 information should be expanded to include:
    - Population health decision makers as discussed previously; and
    - Population health decision influencers, that may not directly manage patient populations, but provide tools and information to population health decision makers. Influencers include:
        - Organizations that develop value frameworks, compendia, and clinical pathways;
        - Organizations that evaluate HCEI
- FDAMA Section 114 information should be presented in a consistent format and process, such as the *AMCP Format 4.0 for Formulary Submissions*, and include leave-behind models when appropriate and permissible under current federal anti-kickback statutes.

AMCP is pleased that the FDA draft guidance largely aligns with the consensus recommendations from the AMCP Partnership Forum. AMCP encourages the FDA to consider the following revisions to the draft guidance:

- Expand eligible recipients of FDAMA Section 114 information to include "population health decision influencers" such as organizations that evaluate HCEI or develop value frameworks and compendia. While population health decision influencers may not directly manage patient populations, they provide tools and information to population health decision makers and would benefit from proactively receiving this information.
- Remove the requirement that information shared under FDAMA Section 114 is considered promotional and therefore subject to post-marketing requirements under 21 CFR 314.81(b)(3)(i). Imposing this

review period would be contrary to the intent of FDAMA Section 114 as updated by Section 3037 of Cures to provide proactive communications for purposes of health care decision making. Furthermore, population health decision makers have the expertise and training to evaluate the information disseminated under this section for credibility, thus making this review process unnecessary. The recommendations from the AMCP Partnership Forum provide an alternative option, such as convening an independent objective entity that would be responsible for developing consensus recommendations for "good research practices" that meet the intent and requirements of these provisions.

After considering comments received, AMCP urges FDA to expeditiously finalize the draft guidance to clarify FDAMA Section 114, as updated by Section 3037 of Cures, to provide the level of clarity necessary for biopharmaceutical manufacturers and population health decision makers to operationalize these proactive communications.

Creation of a Safe Harbor for the Exchange of Clinical and Economic Information for Emerging Therapies Prior to FDA Approval

Current federal laws and FDA regulations significantly restrict communications between biopharmaceutical manufacturers and population health decision makers for emerging therapies prior to FDA approval. Several imperatives are driving the need for communications prior to FDA approval including proper planning, budgeting, and forecasting to accurately account for the impact of new therapies that will enter the market; the successful implementation of value-based payment models; and to account for medications granted breakthrough designation by the FDA that often are approved before clinical trial data is published.

Recommendations from the AMCP Partnership Forum *Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval* include:

- A safe harbor should be established to allow for biopharmaceutical manufacturers to proactively share clinical and economic information about emerging therapies with population health decision makers at least 12-18 months prior to FDA approval. The establishment of a safe harbor is essential to clearly allow the proactive dissemination of this information and clarify that it is not in violation of the prohibition against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.
- Limit exchange to narrow audience: biopharmaceutical manufacturers and population health decision makers only.
- Limit exchange to new molecules and expanded indications with an intent to file only.
- PIE should meet the truthful and non-misleading standard and should be adaptable to include a broad range of information that does not necessarily have to be clinical or scientific evidence, to the extent known and not subject to legal disclosure limitations.
- Exchange of information should be bidirectional and continue until FDA approval.

AMCP urges FDA to expand the scope of preapproval communications to include new indications of approved molecules with an intent to file, and not solely new molecular entities. The draft guidance took a helpful first step in creating a safe harbor for manufacturer communications to payors regarding investigational products. The rationale for such communications, however, applies equally to new indications of products that FDA has already approved for another use. Most, if not all, of the factors mentioned in the guidance (product

information, indication sought, clinical data, anticipated approval timeline, pricing information, targeting/marketing strategies and product related programs or services) are unique to each indication. Anticipating a new indication and properly planning for the impact on budget and expansion of patient populations eligible to receive such medication are vital for payors. Thus to allow payors to prepare for all developments of potential significance to the healthcare market, they need advance information for all new indications, not just for investigational products.

In addition, AMCP urges FDA to work collaboratively with stakeholders and Congress to create a legislative safe harbor for preapproval information exchange by supporting the passage of H.R. 2026 – *The Pharmaceutical Information Exchange (PIE) Act of 2017*. While AMCP was pleased to see that the FDA draft guidance allows the proactive communication of certain information by biopharmaceutical manufacturers to payors prior to FDA approval, the draft guidance remains non-binding and these provisions must be codified by law. Therefore, AMCP encourages the FDA to work with stakeholders and Congress to create a legislative safe harbor for preapproval information exchange so that it is clear that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

In summary, AMCP believes that enabling communications between biopharmaceutical manufacturers and population health decision makers, both pre and post-FDA approval, will help to shift the United States health care system to a focus on value and promote good outcomes for patients. Thank you for the opportunity to provide feedback and for your consideration of our comments. We encourage the FDA to use our organization as a resource as it continues this work.

Sincerely,

Susan A. Cantrell. RPh, CAE
Chief Executive Officer

Attachments:

- Attachment A: AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data. Journal of Managed Care & Specialty Pharmacy 2016 22:7, 826-831
- Attachment B: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval. Journal of Managed Care & Specialty Pharmacy 2017 23:1, 105-112
- Attachment C: Breana Popelar, Soumi Saha, Jay Jackson, Amy Duhig, Matt Sarnes, Stew Kaufman, and Mary Jo Carden. FDAMA 114 for the Exchange of Health Care Economic Information: Payer Experiences, Attitudes, and Perceptions of Current Legislation and Future Directions. Poster session presented at: AMCP Managed Care and Specialty Pharmacy Annual Meeting; 2017 Mar 27-30; Denver, CO. [recipient of silver medal]
- Attachment D: Breana Popelar, Soumi Saha, Jay Jackson, Amy Duhig, Matt Sarnes, Stew Kaufman, and Mary Jo Carden. FDAMA 114 for the Exchange of Health Care Economic Information: Manufacturer Experiences, Attitudes, and Perceptions of Current Legislation and Future Directions. Poster session presented at: AMCP Managed Care and Specialty Pharmacy Annual Meeting; 2017 Mar 27-30; Denver, CO. [recipient of bronze medal]

AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data

SUMMARY

The Food and Drug Administration Modernization Act (FDAMA) of 1997 included Section 114 as a regulatory safe harbor with the goal of increasing the dissemination of health care economic information (HCEI) to those responsible for formulary decision making. HCEI is typically not included within FDA-approved labeling. Although it has been nearly 20 years since passage and enactment of Section 114, proactive distribution of HCEI has been underutilized by biopharmaceutical companies partly because of (a) vague wording in the statute and (b) the absence of FDA-implementing regulations. Consequently, companies and health care decisions makers have had to speculate about the scope of the provisions. As a result, the biopharmaceutical industry has significant concerns about stepping over the line when using the safe harbor. Also, payers and other "payer-like" decision makers (e.g., self-funded corporate insurers) who are trying to make appropriate coverage and utilization decisions are demanding this information but are not receiving it because of the uncertainties in the statute.

Considering this renewed interest by multiple stakeholders regarding the need for revisions and/or guidance pertaining to Section 114, the Academy of Managed Care Pharmacy held a partnership forum on March 1-2, 2016, with a diverse group of health care stakeholders to provide the FDA with considerations for disseminating a guidance document on current thinking for the sharing of HCEI with health care decision makers. Forum participants represented the managed care industry, biopharmaceutical industry, health care providers, pharmacoeconomic experts, policy experts, and patient advocacy groups with specific expertise in the development, use, and dissemination of HCEI. The multistakeholder group represented the key professionals and entities affected by the provisions of Section 114 and present the collective credibility necessary for Congress and the FDA to modernize and operationalize the safe harbor by using the consensus recommendations developed during the forum.

Speakers, panelists, and attendees focused on 4 terms in Section 114 that remain open to interpretation by companies and enforcement bodies: (1) the scope of HCEI, (2) the scope of "formulary committee or similar entity," (3) the definition of "competent and reliable scientific evidence (CRSE)," and (4) the parameters of how information "directly relates to an approved indication." Based on the forum results, it was recommended that the safe harbor for companies' proactive dissemination of information under Section 114 should include health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations. Recommendations also suggested expansion to organizations that evaluate HCEI or develop value frameworks and compendia and individuals in such organizations. Forum participants also recommended that HCEI be truthful, and not misleading, and be based on the expertise of professionals in the relevant area. HCEI must also be developed and disclosed in a transparent, reproducible, and accurate manner.

Forum participants also discussed and agreed on the types of information, format, and processes by which managed care pharmacy and other health care decision makers seek to receive HCEI from biopharmaceutical companies. Finally, participants encouraged the FDA, Congress, and other stakeholders to find ways to ensure that patients or their representative organizations have appropriate access to a full range of information about their medications and that information related to the medication pipeline is communicated to appropriate stakeholders in a timely manner.

J Manag Care Spec Pharm. 2016;22(7):826-31

Health care economic information (HCEI) has long been valued by managed care organizations, payers, pharmacy benefit managers, and other entities that are responsible for drug formulary decision making for its assistance in evaluating the benefits and costs of drugs and health technologies.[1] Nearly 20 years ago, Section 114 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 was instituted to authorize the communication of HCEI between biopharmaceutical companies and formulary committees or similar entities.[2] However, the U.S. Food and Drug Administration (FDA) has yet to release guidance or regulations to provide clarification on this topic; therefore, confusion remains regarding what is permissible under Section 114, leaving interpretation of the statutory language unclear to individual companies and enforcement bodies.

Despite enactment of the law in 1997, proactive distribution of HCEI remains underutilized in large part because of biopharmaceutical companies' concerns that, given the absence of FDA regulations or guidance to clarify the boundaries of the safe harbor, providing economic analysis could result in FDA sanctions for off-label dissemination of information.[1] As biopharmaceuticals become increasingly complex and personalized, and the U.S. health care system becomes increasingly focused on value and quality versus quantity, health care decision makers' evaluation of HCEI for these products is now more important than ever. For these reasons and others discussed in these proceedings, clarification and modernization of Section 114 and/or other laws regarding medical, scientific, and pharmacoeconomic information sharing is necessary to facilitate the communication of evidence for drugs and other health technologies.

Purpose and Discussion Points

To address the clarification and modernization of Section 114, the Academy of Managed Care Pharmacy (AMCP) held a partnership forum on March 1-2, 2016, with a diverse group of health care stakeholders to provide the FDA with considerations for disseminating a guidance document on current thinking for the sharing of HCEI with health care decision makers.

The purpose of the forum was as follows:

1. Provide recommendations to the FDA (to the extent that the forum recommends expansion or change to the statutory safe harbor, then recommendations would be shared with the relevant congressional authorizing committees) for the promulgation of regulations or guidance to provide clarification and consistency of Section 114 requirements:
   - Create definitions for the following terms referenced in Section 114 to clarify what is considered relevant HCEI:
     a. Competent and reliable scientific evidence (CRSE).
     b. Formulary committee or other similar entity.
     c. HCEI.
     d. Directly relates to an approved indication.
   - Articulate the type of information, format, and process by which health care decision makers would like to receive HCEI from biopharmaceutical companies.
2. Consider whether Section 114, or other areas of existing laws and regulations, should be expanded to provide HCEI to additional entities and articulate the value that would be gained. Audiences for consideration include payers, health care providers, accountable care organizations (ACOs), integrated delivery networks (IDNs), patient advocacy groups (PAGs), organizations that develop value frameworks (e.g., American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN], and Institute for Clinical and Economic Review [ICER]), and research societies (e.g., International Society for Pharmacoeconomics and Outcomes Research [ISPOR] and National Pharmaceutical Council [NPC]).

Past, Present, and Future of FDAMA Section 114

Speaker Peter Neumann, director of the Center for the Evaluation of Value and Risk in Health at Tufts Medical Center, opened the forum by providing an overview of the past, present, and future of Section 114. Government regulatory discussions of pharmaceutical promotion and health economic analyses by biopharmaceutical companies began in 1995. This time period also marked the rise of the field of pharmacoeconomics and outcomes research. Organizations that provide and house these types of analyses did not exist at this time. ISPOR, the organization now recognized for advancing the methods of pharmacoeconomics and outcomes research, was just coming into existence. Biopharmaceutical companies began examining what types of drug and health technology information could be actively promoted and in what manner. FDAMA included Section 114 to specify the conditions under which biopharmaceutical companies could promote HCEI.

Although it has been rumored for several years that the FDA would release guidance on Section 114, it has yet to do so.[1] As the interest of managed care organizations, biopharmaceutical companies, and other entities in determining the value of health care interventions by using real-world evidence and comparative effectiveness research continues to increase, the need for clarity is now more important than ever.[3] Many of the terms in Section 114 are not clearly defined in statute or regulations, including the scope of HCEI, the scope of "formulary committee or similar entity," the definition of "competent and reliable scientific evidence," and information included in the term "directly relates to an approved indication." Neumann and Saret (2015) developed hypothetical case studies of 10 categories of HCEI promotions to explore the potential legal and policy implications. These 10 categories included "(1) costing out on-label clinical end points; (2) promotion of a costing exercise to physicians working in an ACO setting; (3) burden-of-illness claims; (4) economic analysis of a formulary restriction policy; (5) extrapolations to doses, populations, or settings not covered in trials; (6) adherence claims; (7) 'utilization of care' as a secondary end point in randomized clinical trials; (8) costing out a competitor drug's adverse event; (9) economic analysis of comparative effectiveness claims using an indirect treatment comparison; and (10) extrapolating from surrogate to long-term outcomes in an economic model," all of which are prime examples of communications sought in the real world.[4]

Moving forward, managed care organizations, biopharmaceutical companies, and other entities are still seeking guidance documents or regulations from the FDA on Section 114. There is a high demand for broader interpretations of Section 114, formal guidance, and regulations, since multiple entities have the need for HCEI in formulary decision making. Additionally, the 21st Century Cures Act (H.R. 6),[5] a bill intended to encourage medical innovation that passed the U.S. House of Representatives in July 2015, contains language that would expand Section 114. A few of these provisions include the following: (1) defining "health care economic information" to acknowledge that all HCEI contains clinical information and allowing companies flexibility around clinical and economic endpoints; (2) disclosure to allow for more transparency of health economic methodology including the analysis and inputs; (3) broadened language to specifically include payers, to suggest that HCEI is not only useful for formulary committees; and (4) "directly relates" was changed to "relates" to suggest that such extrapolations mentioned previously are allowed. Although the 21st Century Cures Act provides more clarity on HCEI, as the U.S. Senate considers similar legislation, it is not certain whether it will contain the language from the House bill. Further, forum participants agreed that while the 21st Century Cures Act was a step in the right direction, it did not provide the level of clarity needed to truly operationalize Section 114, absent guidance or regulations from the FDA. Therefore, it is essential that the FDA avoid any further delays in providing guidance on Section 114.

Current Challenges and Barriers

Currently, significant uncertainties regarding many of the terms stated in Section 114 exist. Challenges and barriers outlined by forum panelists and participants include the following:

- What is the scope of HCEI that can be communicated? One main issue that arises with this statement is that health care economic analyses often contain clinical content, at least at the foundation; therefore, HCEI is not purely an economic claim.
- To whom does "formulary committee or similar entity" refer? Today, health care decision makers include entities that did not exist in 1997, including ACOs and IDNs. "Similar entity" seems to suggest all organizations involved in population health decisions, but this was never specified. Where is the line drawn?
- What constitutes CRSE and how does it differ from the traditional FDA evidentiary "substantial evidence" standard? Section 114 did not specifically define the evidentiary requirements for CRSE, although it is clear that this is a different standard than the "adequate and well-controlled" standard for inclusion of clinical trial information in the FDA-approved labeling. These requirements may include transparency of methodology through "good research practices" (defined by professional societies' guidelines for conducting research) and disclaimers about research and methods, among others. Although professional societies have developed research guideline reports that provide consensus on good research practices, there are many guideline reports from several different professional societies (e.g., ISPOR and AMCP) with guidelines that are not always consistent across reports.
- Does "directly relates" include modeling and extrapolating from intermediate to long-term endpoints or to other subgroups and doses? "Directly relates" seems to suggest that FDAMA 114 is not a vehicle to make HCEI claims beyond the approved indication and the populations or doses in clinical trials.

Given the significant gray areas in Section 114, the evolution of health care since 1997, and the growing need for HCEI by decision makers, clarifying guidance from the FDA is necessary.

HCEI Under FDAMA Section 114

In considering HCEI under Section 114, speakers and panelists discussed how evidence needs have changed since 1997, what constitutes HCEI, how it should be evaluated, and how it is used today. Since 1997, a greater variety of drug and health technologies, at a wider range of prices, have become available. Participants agreed to the following:

- Evidence should be used and shared to provide clarity regarding the value of drugs and other health technologies.
- HCEI includes much more than costs and refers to a broad set of information well beyond the classic randomized controlled trial with limited endpoints and small sample sizes. HCEI includes health care utilization (e.g., hospitalizations and emergency department visits), patient benefits, adherence, endpoint extrapolations, quality of life, and adverse events, in addition to their associated costs.
- Methodology, inputs, and limitations should be transparent. When data are not available and modeling techniques are used, it should be communicated that these models may be used when data are not available but may be updated as information becomes available.
- Evaluation and review are necessary to ensure that scientific evidence is "competent and reliable." Some panelists and speakers suggested that an independent objective body should be responsible for developing consensus recommendations regarding what is considered "good research practice" for CRSE and updating those recommendations on a regular basis as new types of methods and analyses become available. Also mentioned was that HCEI should be evaluated and be made available for formulary decisions.

Suggested Definitions and Rationale for FDA Guidance and Regulation on Terms Used in the Existing Statutory Language of FDAMA Section 114

"Competent and Reliable Scientific Evidence"

Forum participants defined CRSE as "truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on the expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate, and valid."

Rationale:

- The Federal Trade Commission's definition was used as a basis for the Section 114 definition,[9] although there was considerable debate around removing "generally accepted" because it may inhibit the development and use of new studies or data collection methods. As long as innovative methods are transparent, disclosed, reproducible, accurate, and valid, some forum participants noted that CRSE would not need to be "generally accepted."
- "Truthful and non-misleading" was included to reiterate that evidence must be transparent. Although scientific evidence may be competent and reliable, there is still potential for it not to be truthful and to be misleading. In addition, given the constitutional protection for "truthful and non-misleading" communication, this standard should form the basis for permissible information sharing.
- Transparency and disclosure would be met by presenting a full report of the evidence, including the methods, population, and analytic plans, that would be available to decision makers. Additionally, some participants noted that decision makers sometimes request that models be left with them to download, audit, and test, to the extent that this is possible given existing federal fraud and abuse laws.

- The term "reproducible" was a highly debated topic. Panelists and participants noted that a model's results may not be reproducible and including this term may inhibit the use of models. Others debated that the methods should be reproducible, but the results would not be because different data sources (inputs) likely produce different results.
- It was recommended by forum participants that an independent objective entity would be responsible for developing consensus recommendations regarding "good research practices," but this entity would not necessarily be responsible for vetting all HCEI to determine if it is CRSE. However, this independent objective body could be made available to vet HCEI as CRSE should manufacturers need guidance on whether their HCEI meet the standard for CRSE. This entity would consist of a multistakeholder collaborative of representatives from organizations such as AMCP, ISPOR, and NPC, which would conform to requirements under the Federal Advisory Committee Act (FACA).[10]

"Formulary or Other Similar Entity"

Panelists and participants defined "other similar entity" as "health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."

Rationale:

- Examples of "other similar entity" include payers, ACOs, IDNs, and actuaries; pharmacy and therapeutic committees; physician practices involved in risk-sharing arrangements; and organizations that develop compendia, pathways, and/or value frameworks. Flexibility should exist to identify additional entities in the future as the health care environment continues to evolve and as new test models are developed and implemented, such as by the Centers for Medicare and Medicaid Innovation (CMMI).
- Participants debated the option of allowing "no limitations" on the definition of "similar entities" under Section 114, other than that this particular provision would exclude dissemination directly to consumers. Many participants and speakers emphasized that Section 114 is designed to affect decisions related to health care decision making for entities involved in population health and not in direct patient care; therefore, discussion on clarifications should be similarly limited.
- Participants debated whether PAGs should be included as an "other similar entity." Participants in favor of this option suggested that extremely sophisticated PAGs exist and can understand and interpret these data, as well as break the data down to a "patient level." Those not in favor defended the position that there is a potential for abuse as a promotional activity to consumers, and again, that this part of the statute describes the delivery of information designed to affect decisions on population health. Including PAGs as an "other similar entity" is discussed in greater detail later in this report (see the "Recommendations to Congress" section).

"Health Care Economic Information"

Panelists and participants defined HCEI as "any analysis that identifies, measures, or compares the economic, clinical, or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."

Rationale:

- Examples of HCEI include comparative effectiveness research and real-world evidence data. Evidence is presented as a resource used to inform a decision but is not necessarily limited to economic information and includes health care utilization and/or costs.
- Comparative studies should be included under Section 114 as long as the comparator is the standard of care, which may or may not be on-label.
- Unbranded evidence, such as burden of illness claims, needs to be addressed, but perhaps in other laws/regulations, since real-world drug utilization consists of on- and off-label treatments.

"Directly Relates to an Indication Approved"

Panelists and participants defined "directly relates to an indication approved" as "information about a product that may vary from the parameters utilized in a randomized control trial, such as dosage forms, settings, or populations studied," as long as it is still used within the approved disease indication.

Rationale:

- Participants stated that "directly relates" refers to the indication section of the label but does not limit to expanding the population, dosage, or settings within the indication.
- Participants debated the interpretation of "directly" in "directly relates" within Section 114. Some argued that "directly" limits the inclusion of several key attributes of any economic analysis, such as long-term consequences and benefits. Others suggested that Section 114 should be used as a vehicle to describe the real-world use of drugs or therapeutic technologies in individuals only within an approved indication.
- Payers indicated the need for HCEI on pipeline products prior to FDA approval in order to build this information into forecasting and premiums.

Format and Process by Which Managed Care Pharmacy Should Receive HCEI from Biopharmaceutical Companies

Format

Forum participants discussed a format and process by which HCEI could be communicated between managed care organizations and biopharmaceutical companies. Participants discussed using AMCP as a means for housing HCEI. Some participants found AMCP's current dossiers to be an organized and comprehensive resource; however, other participants had little experience with the AMCP dossier process. Therefore, it was noted that this was one approach and one format, but other options exist. As mentioned previously, participants discussed

the possibility of "leave-behind models" that would allow the health care decision maker or entity to download, audit, and test the models. This could also allow for decision makers to modify the assumptions of the model based on their perspectives and their covered populations. Health economic analyses would also be fully disclosed, meaning that bibliography, supporting documents, limitations, and potential biases would be fully detailed. Participants also suggested that leave-behind models might require a safe harbor to provide protection from allegations under the federal anti-kickback statutes associated with the potential that the leave-behind models are of value and could be viewed as potentially inappropriate inducements or incentives to the entity receiving the model.[8]

Process

Taking into consideration all definitions and the format outlined previously, many forum participants encouraged the institution of an objective independent body that would be responsible for developing "good research practice" guidelines for CRSE. Furthermore, participants suggested that a central repository could be implemented once HCEI became available. An alert system could notify covered parties when information is available in the repository to allow people to find promotional material of interest.

Recommendations to Congress to Amend, Provide Clarification, and/or Incorporate Possible Expansion of FDAMA Section 114 or Other Areas of Existing Laws

In addition to the definitions previously outlined, forum participants agreed that "directly relates" should be amended to "relates" under Section 114. "Relates" can also mean a drug or other health technology indication that is not specifically stated in the label. Claims regarding intended indications versus approved indications would have to be specifically addressed by the FDA to provide clarity on what is permissible under this part of Section 114. Furthermore, participants agreed that other amendments to Section 114 would include disclosures of transparency, expansion of additional entities under "other similar entity," and the agreed-upon format and process previously mentioned.

Furthermore, throughout the forum discussion it was discussed that there is need for the FDA and Congress to work together in finding a solution for possibly providing HCEI in 2 additional circumstances. First, because patients increasingly have an economic interest in the value of treatment decisions, there is a need for patients to be able to learn about HCEI in order to be an advocate for their own health care decisions. However, forum participants were cautious to recommend that this type of information be disseminated directly to consumers and debated the appropriate mechanism of making this information available to consumers, such as providing only to PAGs with a certain level of scientific expertise. While no consensus was reached, it was agreed that this area needs to be explored further and that appropriate patient protections would need to be addressed. Second, payers and other entities seek HCEI related to drugs and health care technologies in the pipeline 12-18 months before drug or technology approval. Early dissemination of HCEI would allow payers to build this information into forecasting and premiums, since waiting until approval is often too late. It was agreed that these are important areas of possible expansion for safe harbor, but it may not be within the spirit or original intent of Section 114. Therefore, further discussions in this area as to how other laws or regulations, such as expanding scientific exchange provisions, could be amended to provide this type of access to HCEI for PAGs and pipeline medications are warranted.

Value of Expanding FDAMA Section 114

Revisions or guidance to Section 114 are now more important than ever. Value is increasingly a critical element outlined by private payers and health and human services alike. As biopharmaceuticals become increasingly complex and personalized, and the U.S. health care system becomes increasingly focused on value, it is essential that product value is accurately measured through health economic analyses. Expanding Section 114 would also modernize the statute to align with today's health care system, which now includes a variety of entities, data sources, innovative models, and analytics that did not exist in 1997. Furthermore, expanding Section 114 as previously outlined would allow for better decision making in a collaborative spirit between patients, providers, payers, and other entities.

Information exchange across channels would facilitate a dialogue on the value of a product and further engage more in-depth scientific exchange to address more accurate pharmacoeconomic evaluations. Furthermore, improved dissemination of HCEI to decision makers would drive higher value health care. In its current state, FDAMA Section 114 is too limiting and does not have these intended effects.

Conclusions

Guidance has long been sought by managed care organizations, payers, and drug formulary decision-making entities on FDAMA Section 114. The communication of HCEI is now more important than ever because the products available to treat conditions; available information sources; analytic processes; and the organization, delivery, and reimbursement of health care have vastly evolved in the past few decades. Therefore, now is the time for laws and regulations, even outside of Section 114, to evolve in parallel. The recommendations from this forum's participants to the FDA and Congress to amend, provide clarification to, or expand Section 114 will allow for better decision making in a collaborative environment and ensure appropriate regulatory governance of truthful and nonmisleading HCEI, without interfering with drug and health technology innovation.

Forum Participants

YANJUN (CAROL) BAO, PhD, Senior Director, HCV, Health Economics and Outcomes Research, AbbVie; CHRISTOPHER MICHAEL BLANCHETTE, PhD, MBA, Vice President, Evidence Strategy and Generation, Precision Health Economics (panelist); LAURIE BURKE, RPh, MPH, Founder, Lora Group (panelist); LISA CASHMAN, PharmD, Director Clinical Formulary, MedImpact Health Care Systems (panelist); ELIZABETH J. COBBS, PhD, Executive Director, Center for Observational & Real World Evidence, Merck & Co.; GREGORY DANIEL, PhD, MPH, RPh, Deputy Director, Duke-Margolis Center for Health Policy (panelist); DAN DANIELSON, MS, RPh, Pharmacy Manager, Clinical Services, Premera Blue Cross (panelist); JEFFREY K. FRANCER, JD, MPP, Vice President and Senior Counsel, Pharmaceutical Research and Manufacturers of America (panelist); JENNIFER GRAFF, PharmD, Vice President, National Pharmaceutical Council (panelist); JOEL W. HAY, PhD, MS, MPhil, Professor, University of Southern California (panelist); J. RUSSELL HOVERMAN, MD, PhD, Vice President of Quality Programs, Texas Oncology, Medical Director, The U.S. Oncology Network (panelist); JAY JACKSON, PharmD, MPH, Vice President, Global Health Economics & Outcomes Research, Xcenda; DANIEL C. MALONE, RPh, PhD, FAMCP, Professor, University of Arizona (panelist); JAMES K. MARTTILA, PharmD, MBA, Director, Pharmaceutical Contracting and Formulary Management, Mayo Clinic (panelist); CRAIG MATTSON, MS, MBA, RPh, Senior Director, Formulary Development, Prime Therapeutics; JOAN MCCLURE, MS, Senior Vice President of Clinical Information and Publications, National Comprehensive Cancer Network (panelist); JAY MCKNIGHT, PharmD, BCPS, Director, Clinical Strategies and Formulary Management, Humana (panelist); PHILIP NAUGHTEN, PharmD, Senior Director U.S. Research, Takeda Pharmaceuticals U.S.A.; PETER NEUMANN, ScD, Director, Center for the Evaluation of Value and Risk in Health, Tufts Medical Center (speaker); ELEANOR M. PERFETTO, PhD, MS, Professor, Pharmaceutical Health Services Research, School of Pharmacy, University of Maryland, Senior Vice President, Strategic Initiatives, National Health Council (panelist); CARLY RODRIGUEZ, PharmD, Manager, Clinical Pharmacy Services, OmedaRx; LAURIE WESOLOWICZ, PharmD, Director II, Pharmacy Services Clinical, Blue Cross Blue Shield of Michigan; RHYS WILLIAMS, MSc, DSc, Executive Director, Global Health Economics, Amgen; SUSAN C. WINCKLER, RPh, Esq., Chief Risk Management Officer, Leavitt Partners; LORI ZABLOW-SALLES, Esq., Executive Director, Executive Counsel, Boehringer Ingelheim Pharmaceuticals; and GERGANA ZLATEVA, PhD, Vice President, Payer Insights & Access Lead, Oncology, Pfizer.

AMCP Staff: KEVIN BRUNS, JD, Vice President of Communications & Marketing; SUSAN A. CANTRELL, RPh, CAE, Chief Executive Officer; MARY JO CARDEN, RPh, JD, Vice President of Government & Pharmacy Affairs; CHARLIE DRAGOVICH, BSPharm, Senior Director of Business Development & Strategic Alliances; TERRY RICHARDSON, PharmD, BCACP, Director of Product Development; and SOUMI SAHA, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs.

CORRESPONDENCE: Soumi Saha, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs, Academy of Managed Care Pharmacy, 100 N. Pitt St., Ste. 400, Alexandria, VA 22314. E-mail: ssaha@amcp.org.

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AMCP Partnership Forum: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval

SUMMARY

Current federal laws and FDA regulations have significantly restricted the sharing of clinical and health economic information on biopharmaceuticals that have yet to receive FDA approval. Over the past several years, organizations that make health care coverage decisions, including those that set copayments, premiums, and formulary placement, have expressed a need for receiving this information before approval, as long as appropriate safeguards exist to prevent this information from reaching unintended entities. Population health decision makers have indicated that waiting until FDA approval is often too late for the critical planning, budgeting, and forecasting associated with health benefit design, especially given the recent influx of high-cost medications and scrutiny for better evaluation and preparation. Recognizing that securities laws restrict the disclosure of nonpublic information and may need to be amended, permissible early dissemination would allow population health decision makers to incorporate clinical and economic information for pipeline drugs or expanded indications into financial forecasting for the following year's plan. Access to this information is needed 12-18 months before FDA approval when organizations are deciding on terms of coverage and budgetary assumptions for state health insurance rate filings, Medicare and Medicaid bids, contracts with health care purchasers, and other financial arrangements.

The need for exchange of clinical economic information before FDA approval was first introduced at a previous Academy of Managed Care (AMCP) forum in March 2016, which addressed section 114 of the Food and Drug Administration Modernization Act and the communication of such information after FDA approval. To address preapproval information specifically, AMCP convened a Partnership Forum on September 13-14, 2016. This forum included a diverse group of stakeholders representing managed care, the biopharmaceutical industry, providers, patients, health economists, academia, and others. The multistakeholder group represented the key professionals and entities affected by the federal laws and FDA regulations that restrict the sharing of preapproval information and the collective credibility necessary for proposing this new communication process.

Forum participants primarily focused on 6 items of discussion: (1) creating and defining new terms for how biopharmaceutical manufacturers may provide clinical and economic information 12-18 months before FDA approval; (2) defining the clinical and scientific standards that this information should meet; (3) determining which entities should have access to this information and the value to each; (4) the format and process by which this information should be disseminated; (5) developing definitions for existing terms referenced in current laws, regulations, or guidance documents that would need to be modernized to align with the identified new term; and (6) providing safeguards to prevent this information from reaching unintended entities.

Forum participants selected "preapproval information exchange" (PIE) as the correct term to describe this proposed new communication process and to be inclusive of data from pivotal phase III clinical trials, pharmacoeconomic data, and patient-reported outcomes, as well as other relevant items, including anticipated indications, place in therapy, and routes of administration. Stakeholders agreed that PIE should be truthful, nonmisleading, and include a broad range of information to meet the needs of population health decision makers and health care technology evolution. Recipients of PIE would be limited to population health decision makers who need this information for coverage decisions. The format and process for PIE disseminated should allow for a bidirectional exchange between manufacturers and population health decision makers but should not be proscribed in legislation. Furthermore, new legislative language may be beneficial, since PIE is a novel category of information. New legislation could provide a safe harbor and clarity that PIE does not violate preapproval promotion and the Federal Food, Drug, and Cosmetic Act and its regulations.

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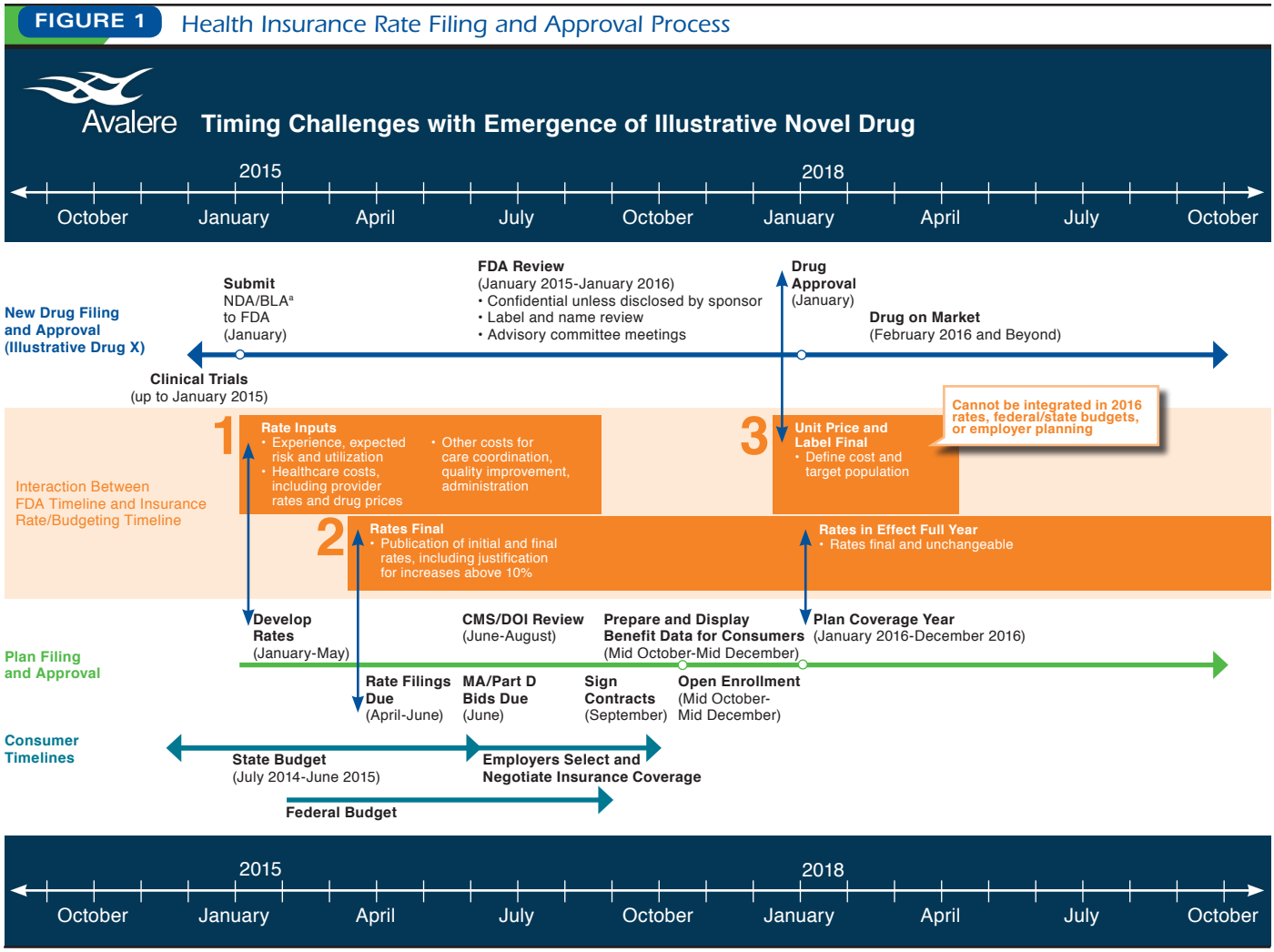
As the U.S. health care system evolves from a historical payment system based on quantity and process to a modernized system rewarding quality and improved patient outcomes, the need for timely communication between biopharmaceutical manufacturers and population health decision makers about emerging therapies is critical for the successful shift to a value-driven system. There are 3 main imperatives driving the need for communications before approval by the U.S. Food and Drug Administration (FDA).[1,2]

First, as a result of new laws such as the Affordable Care Act and state mandates, population health decision makers are required to evaluate their plan designs, formularies, and rates 12-18 months in advance to meet submission deadlines 6-9 months before the beginning of the intended plan year. With rates being filed over a year in advance, proper planning, budgeting, and forecasting are integral for population health decision makers to accurately account for the effect of new therapies that will enter the market. For example, for the 2016 coverage year, population health decision makers analyzed 2014 data in order to submit their 2016 rates by spring 2015 (Figure 1). The budget impact of new therapies that were approved by the FDA after spring 2015 could not be integrated into the 2016 rates. Accurate forecasting and rate setting is critical to ensure that patients have continued access to affordable coverage for their health care needs. Changes are necessary to FDA regulations to expressly permit biopharmaceutical manufacturers to proactively communicate with population health decision makers about emerging therapies before FDA approval so that more accurate forecasting and rate setting are supported, enabling affordable access for all patients to new therapies upon FDA approval.

Second, there is an increased focus on value-based payment models as evidenced by the Medicare Shared Savings Program and a range of initiatives launched and proposed by the Center for Medicare & Medicaid Innovation. Successful implementation of value-based payment models requires understanding the overall value of a therapy, including how pharmacy spending can offset medical costs and vice versa. In addition,

FIGURE 1 Health Insurance Rate Filing and Approval Process



From Eli Lilly and Company and Anthem. Facilitating open communication about emerging therapies. January 29, 2016. Appendix.[2] Reproduced with permission from Eli Lilly and Company.

[a]Median review time 1-2 years.

BLA = Biologic License Application; CMS = Centers for Medicare & Medicaid Services; DOI = Department of Insurance; FDA = U.S. Food and Drug Administration; MA = Medicare Advantage; NDA = New Drug Application.

it requires downstream planning for population health decision makers to change plan design, formularies, and necessary contracts in advance of submitting rates at least a year in advance of the intended coverage year as previously outlined. Therefore, to increase the use of value-based payment models, it is important for biopharmaceutical manufacturers and population health decision makers to be able to share information about emerging therapies before FDA approval in order to provide sufficient time to implement these models in a timely and effective manner upon FDA approval.

Finally, the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) created an expedited approval pathway allowing the FDA to grant priority review if preliminary clinical trials indicate that a therapy may offer substantial treatment advantages over existing options for patients with serious or life-threatening diseases.[3] Under the expedited approval pathway, therapies may be approved by the FDA before clinical trial data are published and made publicly available, thereby making it very difficult for population health decision makers to determine whether a therapy is appropriate for a patient if they receive a coverage request before publication of the data. Guidelines and peer-reviewed compendia sources are even further delayed in providing population health decision makers with reputable reference material for making sound clinical judgements when published clinical data are not available. In these situations, enabling preapproval information

TABLE 1 FDA Guidance and Other Initiatives Regarding Clarification of the Dissemination of Off-Label Drug Information

Year	Topic	Title (if applicable)
1997	Guidance on the scientific exchange of original trial results and off-label information	Industry-Supported Scientific and Educational Activities[4]
2009	Guidance on the distribution of peer-reviewed scientific and medical publications regarding unapproved new uses of approved drugs and approved/cleared medical devices	Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices[5]
2011	Guidance reflecting responses to unsolicited requests	Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices[6]
2011	MIWG petition regarding clarification on off-label communication	Citizen Petition, FDA-2011-P-5012[9]
2013	MIWG petition requesting a constitutional response to 2011 petition (above)	Citizen Petition, FDA-2013-P-1079[10]
2014	Update to 2009 guidance	Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices[7]
2015	Declaration that detailed the FDA's initiatives to accommodate policies to foster stakeholder interests in off-label communication	Declaration by Janet Woodcock[11]

FDA = U.S. Food and Drug Administration; MIWG= Medical Information Working Group.

exchange (PIE) is critical to ensuring that population health decision makers are aware of the information available to date on emerging therapies granted breakthrough designation by the FDA so that they are prepared to make coverage decisions for patients immediately upon FDA approval.

Restricting Information Dissemination

Current federal laws and FDA regulations have significantly restricted communications between biopharmaceutical manufacturers and population health decision makers for emerging therapies before FDA approval, despite clear recognition that budgeting and forecasting by payers is critical to ensure that patients have access to new treatments as soon as possible following market approval. Over the past 3-4 decades, the FDA has disseminated various policy documents addressing this issue.[4-7] While safe harbors for off-label communication already exist, the interpretation is unclear, and enforcement involves various entities with differing approaches (i.e., Health and Human Services Office of the Inspector General, Federal Trade Commission, Department of Justice, and state governments).[8] FDA regulations ensure access to safe and effective medications, while other agencies must ensure prevention of fraud, waste, and abuse, and marketplace competition. Uncertainty regarding safe harbors and the fear of enforcement has limited the dissemination of preapproval information by manufacturers, despite population health decision makers and others expressing a strong need for this information much earlier in the drug development process. There is a definitive need to refine and clarify laws governing activities under the purview of the FDA to help diminish concerns about the possibility of legal action by other agencies. More recently, the FDA has drafted guidance to take steps to support solutions to distinct, yet related, communication challenges; granted petitions to elucidate on this topic; and announced a public hearing to review policies and clarify standards for off-label communication.[4-11] This topic has also been heavily discussed outside of the FDA, including at AMCP's FDAMA Section 114 forum, 21st Century Cures proposals for reform of Section 114, Biotechnology Innovation Organization and Pharmaceutical Research and Manufacturers of America's principles on responsible sharing for truthful and non-misleading information, among others (Table 1).[12-14]

Given these circumstances and others discussed in the following proceedings, further recommendations, guidance, and legislation are needed to provide clarity on the dissemination of information before FDA approval.

Forum Purpose and Discussion Points

To address the long-debated issue of proactive dissemination of clinical and health economic information on products before FDA approval, the Academy of Managed Care Pharmacy (AMCP) held a Partnership Forum on September 13-14, 2016, in Tysons Corner, Virginia, with a diverse group of health care stakeholders to provide recommendations for Congress and the FDA. The purpose of this forum was to discuss the following 6 items:

1. The term that would be used to describe the ability of biopharmaceutical manufacturers to proactively share clinical and economic information about medications in the pipeline with payers and other entities before FDA approval.
2. The standards that clinical and economic information should meet before FDA approval.
3. Stakeholders who should have access to clinical and economic information before FDA approval and the value of this information to each of these entities or individuals.
4. The preferred format and process by which eligible entities would like to receive clinical and economic information from biopharmaceutical manufacturers before FDA approval.
5. The definitions for existing terms referenced in current laws, regulations, or guidance documents (i.e., labeling, misbranded, or intended use) that would need to be modernized to align with the identified new term for the exchange of clinical and economic information before FDA approval.

TABLE 2 Summary of the AMCP FDAMA 114 Partnership Forum[12]

Objective	AMCP convened a Partnership Forum for stakeholders to discuss clarification and possible expansion of FDAMA Section 114 to obtain consensus recommendations on how information related to this statute should be disseminated.
Key stakeholders	Pharmaceutical industry, managed care industry, health care providers, pharmacoeconomic experts, health policy experts, and patient advocates

Recommendations: Terms, Definitions, and Key Points

Term	Definition	Key Points
Competent and reliable scientific evidence	"Truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on the expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate, and valid."	Models would be left behind with reproducible methods.
Formulary or other similar entity	"Health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."	• "Other entity" needs to be flexible as the health care industry evolves over time. • The role of the individual needs to be a key consideration. • Inclusion of patient advisory groups was debated, since some of these groups are sophisticated and have the ability to interpret this information, but not all do, so proper protections need to be considered.
Health care economic information	"Any analysis that identifies, measures, or compares the economic, clinical, or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."	Includes noneconomic information as well, since clinical and quality life endpoints are a part of economic evaluation.

AMCP=Academy of Managed Care Pharmacy; FDAMA=Food and Drug Administration Modernization Act; HCEI=health care and economic information.

6. The public health protections that should be considered to prevent the dissemination of clinical and economic information to unintended entities before FDA approval.

AMCP previously held a Partnership Forum in March 2016 to address communications of health care economic information (HCEI) after FDA approval. More specifically, the March forum discussed the clarification and possible expansion of Section 114 of the Food and Drug Administration Modernization Act (FDAMA) to obtain consensus recommendations on how information related to this statute should be disseminated.[12] While the recommendations from the March forum (Table 2) were focused on HCEI dissemination after FDA approval, a key recommendation was that further discussion was warranted to create recommendations for information exchange before FDA approval.

Stakeholders participating in the September Partnership Forum on preapproval communications were separated into 3 groups. Throughout the forum, each group, which was composed of representatives from the biopharmaceutical industry, payers, provider organizations, academia, health economists, and patient advocacy groups, among others, began its discussion with the question of whether the recommendations from the March forum on post-FDA approval communications were applicable to pre-FDA approval communications or whether the latter required adjustments given the differences in purpose and use before versus after FDA approval. The following recommendations and discussion points are reported to reflect where there was agreement, and where further discussion is warranted.

Terminology to Describe the Sharing of Preapproval Clinical and Economic Information

When considering the terminology that should be used to describe the ability of biopharmaceutical manufacturers to proactively share clinical and economic information about medications in the pipeline with payers and other entities before FDA approval, debate among the 3 groups focused on 3 areas: (1) the term "preapproval," (2) whether the information to be communicated should be information or evidence, and (3) whether the method of conversation should be deemed an exchange or information sharing.

Preapproval

The groups discussed the need for a term that is narrow enough to be included in legislation or adopted in guidance. Whether to include "preapproval" in this term was debated. Stakeholders reached consensus that the final recommended term should differentiate what type of information is to be shared. Including the word "preapproval" in any such term would highlight that the term refers to information disclosed for forecasting, planning, and budgeting before FDA approval. A key point of discussion was when pricing information would be available for medicines initially entering the market. Some stakeholders noted that pricing may only be known shortly, if not immediately, before product launch, while other stakeholders expressed an interest in receiving pricing information, or at least a range of possible prices, as early as possible. Stakeholders recognized, however, that manufacturers must

comply with securities and trade secrets laws that restrict the dissemination of material nonpublic information, which could include pricing, as well as certain clinical trial data.

Information Versus Evidence

The terms "information" and "evidence" were used to describe the clinical and economic data to be communicated. Although the term "scientific information" was proposed, stakeholders agreed that this term may be misinterpreted as being limited to research studies subject to scientific rigor, when instead, the proposed term should be inclusive of additional purposes (e.g., identifying potential patient-populations, distribution requirements, and budgeting). Some stakeholders indicated that as biopharmaceuticals move through the early phases of development, information builds over time and eventually leads to a body of evidence in the later phases of development and throughout the product life cycle. Furthermore, the term "information" was deemed appropriate by some because "evidence" may be viewed as only the types of data that involve a statistical comparison and may limit the use of models and valuable cost analyses. Stakeholders expressed that models cannot be classified as evidence, since they are simply tools to develop estimations, and there was a strong concern among many stakeholders that deeming a model as evidence would lead to misinterpretation as to what such models can and cannot demonstrate and depict from a level of certainty. Those who supported use of the term "evidence" stated that "information" is a broader and more encompassing term that may not have as much weight in the scientific community. The concept of information versus evidence is discussed in more detail throughout this proceedings document.

Exchange Versus Information Sharing

The third area of discussion focused on the terms "exchange" versus "information sharing." Supporters of the term "exchange" felt that the use of this term would signify bidirectional conversations between decision makers and manufacturers and reinforce an ongoing dialogue between the 2 parties. Proponents of the term "information sharing" thought that the term "exchange" would be confused with scientific exchange, which has traditionally been interpreted to be applicable to investigational new drugs under 21 CFR 312.7(a) and therefore expressed hesitance in using this term.

After thorough discussion, stakeholders agreed on the term "preapproval information exchange" (PIE), which referred to the proactive sharing of clinical and economic information by manufacturers to decision makers (entities are discussed later in the proceedings) at least 12-18 months before FDA approval and the ongoing discussions between the 2 sharing entities as information evolves into evidence throughout drug development. Furthermore, stakeholders agreed that this preapproval communication only applies to those biopharmaceutical manufacturers who intend to file for a new indication (new molecules and new indications), thereby limiting the risk for off-label promotion. Stakeholders agreed that the intent of a biopharmaceutical manufacturer to file would need to be justified by submission of an Investigational New Drug (IND) application, New Drug Application (NDA), Supplemental New Drug Application (sNDA), or other similar steps.

Standards for Preapproval Information

Discussion on the question "What standards should clinical and economic information shared prior to FDA approval meet?" began with the definition of "competent and reliable scientific evidence" as developed in the FDAMA 114 forum (Table 2) and how to differentiate the preapproval setting from the postapproval setting. Overall, stakeholders agreed that the standards for this information should be based on the FDAMA 114 forum definition, with a few proposed exceptions:

- "Information" should be either added to the definition or should replace "evidence."
- A minimum set of standards should be set for this information, but as a biopharmaceutical product approaches approval, the information would become stronger and evolve into evidence.
- It was emphasized that because the information about a product could change and augment over time, any disclosure of information for PIE purposes needed to include transparency regarding the methods and results (all of which would need to be done in a truthful and non-misleading manner) with appropriate disclosures of uncertainty and limitations inherent in such information, and methods would need to be reproducible—not the results).

Some stakeholders expressed that all-inclusive information sharing, with ultimately no restrictions, may allow too much lenience, while being too specific may inhibit manufacturers from sharing important information with population health decision makers that would be of value to their decisions and ultimately be important for planning and forecasting purposes. As mentioned in the previous section, limiting the standards to "evidence" may cause legal concern and be interpreted as requiring a level of research or replicability for all information disclosed, which might be unattainable at certain stages of the product's development, whereas the intent is to be able to include additional items such as anticipated indications, place in therapy, routes of administration, distribution channels, and potential budget impact.

Entities and Individuals Who Should Receive Preapproval Information

During the FDAMA 114 forum, it was decided that entities who should receive HCEI after FDA approval would be "health care decision makers beyond health plan formulary

committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations" (Table 2). Stakeholders were asked to consider these same entities for preapproval purposes, in addition to pharmacy and therapeutic committees, managed care pharmacy, health care providers, accountable care organizations (ACOs), integrated delivery networks, patient advocacy groups (PAG), organizations that develop value frameworks (e.g., American Society of Clinical Oncology and National Comprehensive Cancer Network), organizations that develop clinical practice guidelines (e.g., American College of Cardiology and American Diabetes Association), research societies (e.g., International Society for Pharmacoeconomics and Outcomes Research), actuaries, contract specialists, and others.

All stakeholders agreed that population health decision makers such as managed care organizations and pharmacy benefit managers would be eligible to receive preapproval information. In addition, certain integrated delivery networks (IDNs) and ACOs that bear financial risk for biopharmaceuticals would also be eligible to receive preapproval information. These population health decision makers were included because entities and individuals within these organizations need to receive this information in advance of FDA approval for budgeting, forecasting, and coverage decision purposes.

Forum stakeholders also considered whether other entities that are "influencers," such as groups that develop value frameworks and clinical practice guidelines should be included in PIE. Some stakeholders thought that clinical practice guidelines developers would need to know this information, since the evolution of guidelines is a lengthy process, and it would be beneficial to know this information for the next guideline update. A limited number of stakeholders thought that some benefit exists in expanding this information sharing to PAGs, since the FDA is moving toward more patient-focused drug development. However, the majority of stakeholders strongly argued that the need for HCEI is for entities that have accountability for forecasting costs to ensure patient access and coverage, which is not the case for influencers or PAGs. While preapproval information sharing with influencers and PAGs was considered, there was consensus that the pre-FDA approval information most valuable to influencers and PAGs was clinical in nature, not preliminary economic or financial data. Furthermore, entities such as influencers or PAGs could receive this information through the usual channel of unsolicited requests. Therefore, the majority of stakeholders agreed that only entities who manage a population's health should receive preapproval information.

Preferred Format and Process for Receiving Preapproval Information

After reviewing the recommendations set forth at the FDAMA 114 forum, stakeholders were asked the question "What is the preferred format and process by which eligible entities would like to receive clinical and economic information prior to FDA approval from biopharmaceutical manufacturers?". Overall, stakeholder consensus supported the creation of a flexible means of providing this information that allows for a bidirectional exchange between manufacturers and population health decision makers and that a specific format or process should not be prescribed in legislation. Furthermore, AMCP was identified as a potential driver and leader in this space, given that AMCP has an established process for communication of information about biopharmaceutical products to inform decisions made by formulary committees. This process is currently restricted to unsolicited requests but could be adapted for PIE. Conversely, a few key points were debated:

1. *Central repository versus repositories for each manufacturer.* Some stakeholders thought that having multiple repositories (each for a different biopharmaceutical manufacturer) would simplify the risk of unintended users gaining access to preapproval information. Others stated that having the ability to compare medications and technologies in a central repository during a single log-in would allow for a more simplified, effective process. The central repository would allow for alerts once information is updated—decision makers could choose to opt-in and the frequency of the alerts they would like to receive (e.g., once a month or once a week). Later in the discussion, stakeholders noted that AMCP already has a central repository system in place for dossier submissions and viewing; therefore, this same system could be adapted as an option for communicating information in the preapproval setting.
2. *Standardized format versus flexible format.* An AMCP dossier-light format was initially suggested by many stakeholders, while others were concerned that not all end users, such as IDNs and ACOs, would be as familiar with this format; therefore, the format would need to be adaptable and flexible to suit the needs of organizations or entities. Furthermore, technology is rapidly evolving and developing, so a format developed today may not be useful tomorrow. Others disagreed, stating that a standardized format with the ability to locate the same information in the same location between 2 products would allow for a more simplified, consistent process.
3. *Communication and notification.* Communications via a repository would include notifications to decision makers once information was updated, options for manufacturers to share models and slide-decks, and one-on-one conversations between manufacturers and decision makers. More importantly, manufacturers and decision makers would have the option to choose the type and frequency of

engagement, depending on their individual needs, and whether to use a central repository or another process for exchanging this information.

Stakeholders ultimately agreed that the forum discussion is a starting point for the consideration of format options and that a specific format or process should *not* be prescribed in legislation but should be developed collaboratively between the manufacturers and population health decision makers who would be exchanging this information. The group agreed that given AMCP's history of providing this type of information, it is in a good position to serve as a leader and developer for providing information under PIE.

Definitions for Existing Terms in Current Laws, Regulations, or Guidance Documents

Given the existing terms included in current laws, regulations, and guidance documents, stakeholders were asked the question "How should the definitions for existent terms, referenced in current laws, regulations, or guidance documents (such as labeling, misbranded, or intended use) be modernized to align with the identified new term for the exchange of clinical and economic information before FDA approval?". Stakeholders quickly reached a consensus that PIE would need to have its own safe harbor, in a manner consistent with existing law.

Public Health Protections to Prevent the Dissemination of Preapproval Information

Stakeholders considered the public health protections required to prevent the dissemination of preapproval information and agreed that it should function similarly to the system in place for HCEI under FDAMA Section 114. The stakeholders agreed that certain public health protections are already in place through other legislation, so there may not be a need to create further protections beyond those already enacted.

Conclusions

Currently, the sharing of clinical and health care economic information on new products and indications before FDA approval is significantly restricted by federal laws and FDA regulations regarding product promotion. Population health decision makers have expressed a need for receiving this information at least 12-18 months before FDA approval to properly plan, budget, forecast, and care for the populations they serve, as long as safeguards are in place to prevent preapproval information from reaching unintended entities. The recommendation from this Partnership Forum is for Congress to establish a safe harbor for preapproval information exchange between biopharmaceutical manufactures and population health decision makers to encourage better decision making, without interfering with innovation in the biopharmaceutical and health technology industry.

Forum Participants

ALEXIS AHLSTROM, MPH, Director, GlaxoSmithKline; ANDREW BEHM, PharmD, CGP, Vice President, Express Scripts; CHRISTOPHER MICHAEL BLANCHETTE, PhD, MBA, Vice President, Evidence Strategy & Generation, Precision Health Economics, Associate Professor, Public Health Sciences, University of North Carolina at Charlotte; ELIZABETH L. BRUSIG, PharmD, MBA, Clinical Pharmacy Specialist, Optima Health Plan; SUSMITA CHAVALA, PharmD, MHA, Senior Principle, Clinical Policy, Prime Therapeutics; GREGORY DANIEL, PhD, MPH, RPh, Deputy Director, Duke-Margolis Center for Health Policy; AMY DUHIG, PhD, Senior Director, Outcomes Research, Xcenda; PAUL EITING, MPP, Senior Manager, Value-Based Policy, Blue Cross Blue Shield Association; ELIZABETH ENGELHARDT, RN, BSN, Head of Specialty Strategy & Clinical Management, Aetna; JEFFREY K. FRANCER, JD, MPP, Vice President and Senior Counsel, Pharmaceutical Research and Manufacturers of America; JENNIFER GRAFF, PharmD, Vice President, Comparative Effectiveness Research, National Pharmaceutical Council; JOEL W. HAY, PhD, MS, MPhil, Professor, University of Southern California; DOROTHY HOFFMAN, MPP, Director, Global Public Policy/Head, U.S. Health Policy, Eli Lilly and Company; KAT WOLF KHACHATOURIAN, PharmD, Vice President, Pharmacy Services & Strategy, Qualchoice Health Plan Services; CRYSTAL L. KUNTZ, MPA, Vice President, Policy and Regulatory Affairs, America's Health Insurance Plans (AHIP); JEFF LEE, PharmD, FCCP, Associate Professor, Pharmacy Practice, Lipscomb University College of Pharmacy; ERIN LOPATA, PharmD, Manager of Clinical Pharmacy, UPMC Health Plan; JAMES K. MARTTILA, PharmD, MBA, Director, Pharmaceutical Contracting and Formulary Management, Mayo Clinic; JOAN S. MCCLURE, MS, Senior Vice President of Clinical Information and Publications, National Comprehensive Cancer Network; NEWELL MCELWEE, PharmD, MSPH, Associate Vice President, Center for Observational and Real World Evidence, Merck; COREY PELLETIER, PhD, Director, US Health Economics & Outcomes Research, Celgene; ELEANOR M. PERFETTO, PhD, MS, Professor, Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Senior Vice President, Strategic Initiatives, National Health Council; MICHAEL RYAN, PharmD, Senior Vice President, Value Access & Payment, Bristol-Myers Squibb; SHEILA M. THOMAS, PharmD, Senior Director, Evidence Based Medicine, Sanofi; ROBIN S. TURPIN, PhD, Lead Director, HEOR, Takeda Pharmaceuticals, USA; ANTHONY WANG, PhD, MPH, Senior Manager HEOR, AbbVie; MELEA WARD, PhD, PharmD, BCPS, Director, Outcomes and Evidence, Pfizer Oncology; JAMES WEATHERALL, BBA, MA, PhD, Director, Health Economics & Outcomes Research, Novo Nordisk; SUSAN C. WINCKLER, RPh, Esq., Chief Risk Management Officer, Leavitt Partners; KRISTINA YU-ISENBERG, PhD, MPH, RPh, Vice President and Head, Evidence Generation and Analytics, Intarcia Therapeutics; and LORI ZABLOW-SALLES, Esq., Executive Director, Executive Counsel, Boehringer Ingelheim Pharmaceuticals.

AMCP STAFF: SUSAN A. CANTRELL, RPh, CAE, Chief Executive Officer; MARY JO CARDEN, RPh, JD, Vice President of Government & Pharmacy Affairs; CHARLIE DRAGOVICH, BSPharm, Senior Director of Business Development & Strategic Alliances; ASHLEY LANHAM, PharmD, MBA, Manager of Student Development & New Practitioner Programs; and SOUMI SAHA, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs.

CORRESPONDENCE: Soumi Saha, PharmD, JD, Assistant Director of Pharmacy & Regulatory Affairs, Academy of Managed Care Pharmacy, 675 N. Washington St., Ste. 220, Alexandria, VA 22314. E-mail: ssaha@amcp.org.

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FDAMA 114 for the Exchange of Healthcare Economic Information: Payer Experiences, Attitudes, and Perceptions of Current Legislation and Future Directions

Breanna Popelar[1], Matt Sarnes[1], Amy Duhig[1], Stew Kaufman[1], Jay Jackson[1], Soumi Saha[2], Mary Jo Carden[2]
[1]Xcenda, LLC; [2]Academy of Managed Care Pharmacy

BACKGROUND

- Section 114 of the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA 114) was intended to permit the transfer information beyond efficacy and safety data and allow for payer receipt of HCEI to help inform formulary decision making. However, the section's language is vague and, in the absence of formal FDA guidance or clarifying statements over the past 20 years, minimal HCEI has been shared promotionally under FDAMA 114.[1-3]
- In December 2016, the 21st Century Cures Act sought to clarify the original provision by clarifying the definition of HCEI, expanding the target audience for receiving HCEI, broadening the range of information shared with payers, and requiring clear statements related to the differences between HCEI and approved labeling.
- Additionally, in January 2017, the FDA issued draft HCEI guidance on the specific types of information that are considered to be "related" to an approved indication, contextual information that should be included when disseminating HCEI, and guidance on pre-approval dissemination of HCEI for investigational drugs and devices.

OBJECTIVE

- To understand payer experiences, attitudes, and perceptions of FDAMA 114 and help shape future regulatory guidance for the proactive dissemination of HCEI.

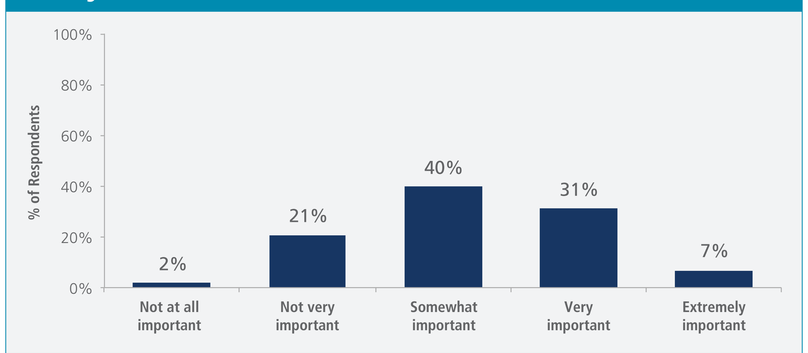
METHODS

- Payer stakeholders completed an online 31-item survey in November and early December 2016 (11/18/16 to 12/12/16) in advance of the passing of 21st Century Cures and the January release of the FDA draft guidance.
- Survey links were sent to members of the Academy of Managed Care Pharmacy (AMCP) with additional outreach to payer contacts from Xcenda's Managed Care Network.
- The survey included questions on the use and importance of HCEI in formulary decision making, unmet needs for HCEI, variation and utility of HCEI from manufacturers, and limitations and impact of AMCP-proposed changes to Section 114.

RESULTS

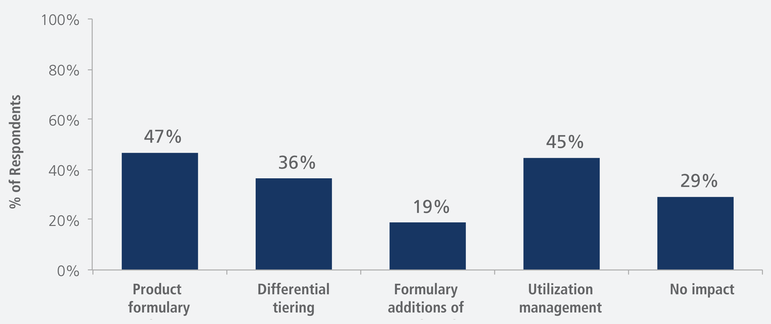
- Respondents (N=58) were largely from managed care organizations (76%), pharmacy benefit management (19%), and/or integrated delivery network (17%) organizations, representing approximately 185M covered lives.[a] Most (66%) served as voting Pharmacy and Therapeutics Committee members. Respondents included pharmacy directors (57%), medical directors (29%) and others (14%) with both national (29%) and regional (71%) representation. All were directly involved in medical policy, formulary decisions, and/or tracking utilization management within their organization.
- The majority ranked HCEI as somewhat to extremely (78%) important for formulary or medical policy decisions (**Figure 1**) and 78% thought that the importance of HCEI would increase in the next 3-5 years. About one-fifth of respondents (21%) thought the importance of HCEI in formulary decision making would not change over the next 3-5 years and 2% thought the importance would decrease very much.

Figure 1. Importance of HCEI in Formulary or Medical Policy Decisions



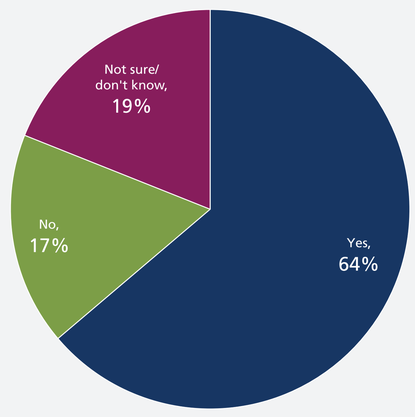
- As seen below, respondents indicated that HCEI has impacted decisions in various aspects of the formulary decision-making process (**Figure 2**).

Figure 2. Use of HCEI to Support Various Aspects of Formulary Decision Making



- However, only 7% of respondents reported including HCEI in >75% of product discussions, with 12% using HCEI in 51 to 75% of discussions, and the majority (76%) of respondents including HCEI for ≤50% of products discussed over the past 6 months.
- Over 60% noted a gap between their need for HCEI vs what has been available to them and shared that product decision making would be very much or extremely improved (54%) if the gap between HCEI needed for formulary decision-making and available HCEI were addressed (**Figure 3**).

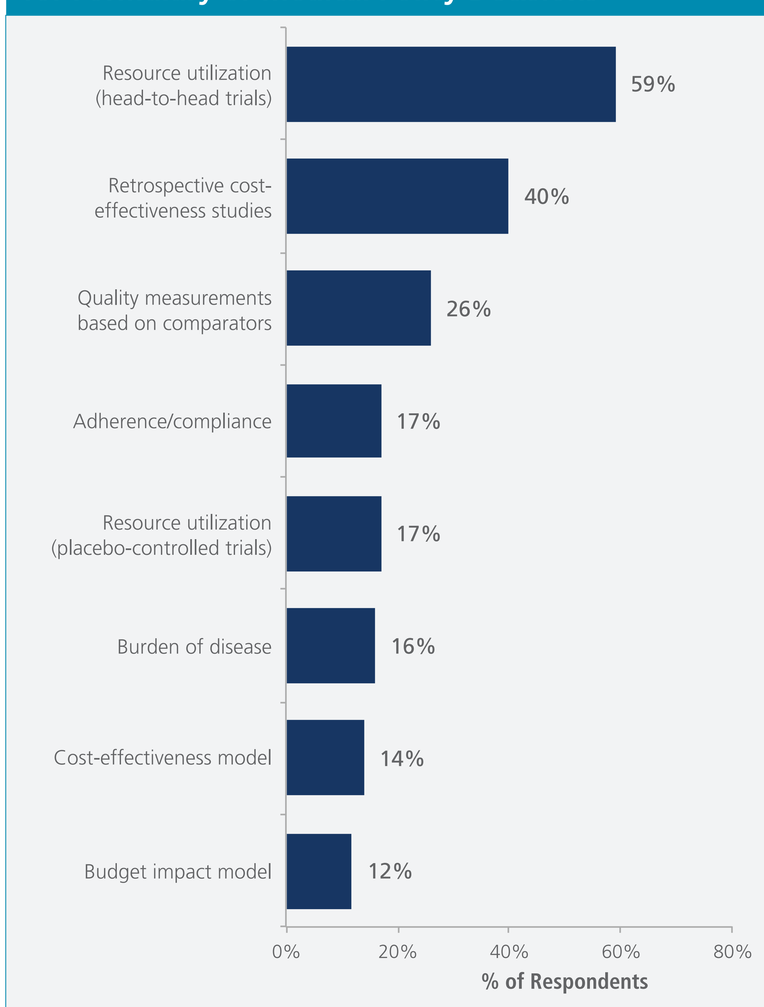
Figure 3. Perceived Gap Between Needed and Available HCEI



54% of respondents indicated that decision making would be very much or extremely improved if the gap between needed and available HCEI was addressed

- Resource use data from head-to-head trials (69%) and retrospective studies comparing effectiveness and costs (64%) were the types of HCEI most commonly rated as very or extremely useful for formulary or medical decision making.
- Additionally, payers ranked various types of HCEI as most important for formulary or medical policy decision making. As seen in **Figure 4**, resource use data from head-to-head trials was most commonly ranked as most important for formulary or medical policy decision making.

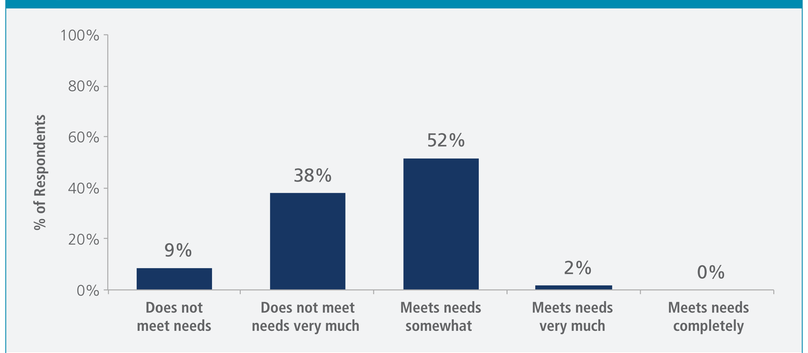
Figure 4. Types of HCEI Ranked^ as Most Important for Formulary or Medical Policy Decisions



^Ranked as 1 or 2.

- As seen in **Figure 5**, HCEI provided from manufacturers in response to unsolicited requests typically met payer needs only somewhat or not very much.

Figure 5. Degree of Manufacturer HCEI Meeting Payer Needs



- Many payers (40%) felt that proactive exchanges of HCEI via a structured AMCP dossier-like format would be very or extremely helpful.
- Medical outcomes liaisons and medical science liaisons were considered very or extremely reliable to deliver HCEI, according to respondents. Payers were less comfortable with delivery of HCEI by account managers and sales representatives, as shown in **Figure 6**.

Figure 6. Proactive Delivery of HCEI by Manufacturers

Manufacturer representatives considered very or extremely reliable to deliver HCEI as rated by payers

- With regard to the changes proposed in a March 2016 AMCP Partnership Forum to add clarity to FDAMA 114 (**Table 1**), the majority (52% to 66%) very much or completely agreed that the suggested changes would be helpful in improving their organization's ability to effectively communicate HCEI. Note that the 21st Century Cures Act enacted in December 2016, after the collection of this survey data, implemented changes to the original FDAMA 114 language to add clarity, some of which were in alignment with AMCP recommendations.

Table 1. Proposed Changes to FDAMA 114 Language

FDAMA 114 Language	AMCP Partnership Forum Proposed Changes
"Competent and reliable scientific evidence"	"Truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate and valid."
"Formulary or other similar entity"	"Health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."
"Health care economic information"	"Any analysis that identifies, measures, or compares the economic, clinical or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."
"Directly relates to an approved indication"	"Information about a product that may vary from the parameters utilized in a randomized controlled trial, such as dosage forms, settings, or populations studied, as long as it is still used within the approved disease indication."

CONCLUSIONS

- While the use of FDAMA 114 has been limited over the past 20 years, the evolving value-driven healthcare environment and recent legislative updates have spawned renewed interest in the exchange of HCEI.[2]
- Recent approval of 21st Century Cures and the January 2017 FDA guidance provided some clarity and may improve the effective exchange of HCEI among payers and manufacturers, but to what extent is unclear. The content and impact of the finalization of FDA's guidance, expected this fall, is also uncertain. Regardless, this research reinforces that despite the importance of HCEI in payer decision-making, availability and communication of HCEI from manufacturers is varied and limited. Additionally, this research has implications for the type of data that may be considered for generation by manufacturers and the types of manufacturer representatives who should deliver HCEI proactively.
- Limitations of this analysis include lack of stratification by disease state, brand vs generic products, etc. Future research may provide additional insight into potential nuances underlying the results.
- Addressing the gap between available and desired HCEI may significantly improve payers' formulary decision-making ability.

REFERENCES

1. Neuman, PJ, et al. *Value Health*. 2015;18:682-689.
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3. AMCP Partnership Forum: FDAMA Section 114—improving the exchange of health care economic data. *J Manag Care Spec Pharm*. 2016;22(7):826-31.

[a]Note the number of covered lives represented is likely overstated as multiple individuals from one organization may have responded to the survey.

SPONSORSHIP

- None. This research was conducted by Xcenda, LLC in partnership with the Academy of Managed Care Pharmacy.
- The authors would also like to recognize Jasmine Knight, PharmD, MS and Kellie Meyer, PharmD, MPH for their contributions to this analysis.

FDAMA 114 for the Exchange of Healthcare Economic Information: Manufacturer Experiences, Attitudes, and Perceptions of Current Legislation and Future Directions

Breanna Popelar[1], Soumi Saha[2], Jay Jackson[1], Amy Duhig[1], Matt Sarnes[1], Stew Kaufman[1], Mary Jo Carden[2]
[1]Xcenda, LLC; [2]Academy of Managed Care Pharmacy

BACKGROUND

- Section 114 of the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA 114) was intended to allow the sharing of healthcare economic information (HCEI) with formulary decision makers. However, the section's language is vague and, in the absence of formal FDA guidance or clarifying statements over the past 20 years, manufacturers have struggled with interpretation and application of the legislation.[1-3]
- In December 2016, the 21st Century Cures Act sought to clarify the original provision by clarifying the definition of HCEI, expanding the target audience for receiving HCEI, broadening the range of information shared with payers, and requiring clear statements related to the differences between HCEI and approved labeling.
- Additionally, in January 2017, the FDA issued draft HCEI guidance on the specific types of information that are considered to be "related" to an approved indication, contextual information that should be included when disseminating HCEI, and guidance on pre-approval dissemination of HCEI for investigational drugs and devices.

OBJECTIVE

- To understand manufacturer experiences, attitudes, and perceptions of FDAMA 114 and help shape future regulatory guidance on the proactive dissemination of HCEI.

METHODS

- Manufacturer stakeholders completed an online 23-item survey in November and early December 2016 (11/18/16 to 12/12/16) in advance of the passing of 21st Century Cures and the January release of the FDA draft guidance.
- Survey links were sent to members of the Academy of Managed Care Pharmacy (AMCP) with additional outreach to manufacturer contacts by Xcenda.
- The survey included questions on the process for and consistency of approval of FDAMA 114 materials, types of HCEI approved for use under FDAMA 114, FDAMA 114 stakeholders, and limitations and impact of AMCP-proposed changes to Section 114.

RESULTS

- Respondents (N=73) represented small- to large-sized companies, with representation primarily from health economics and outcomes research (HEOR), medical affairs, and managed markets/market access functions (**Figure 1**). Respondents were primarily Associate Director level or above (**Figure 2**).

Figure 1. Role in Organization

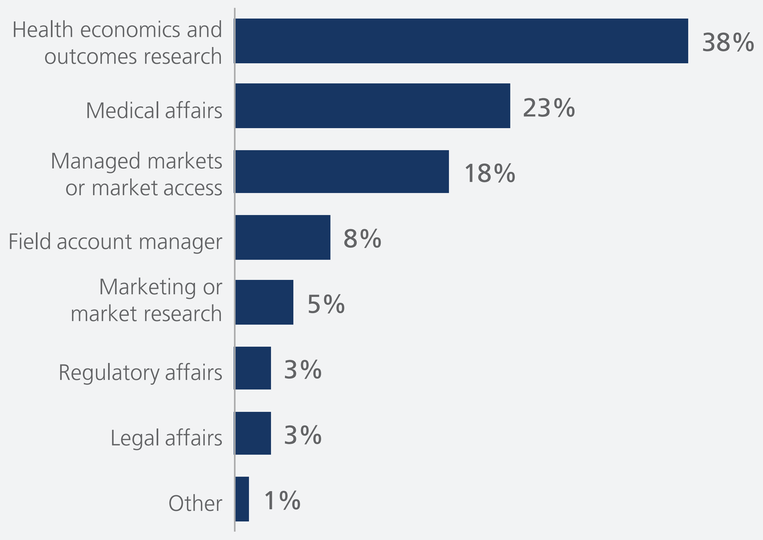
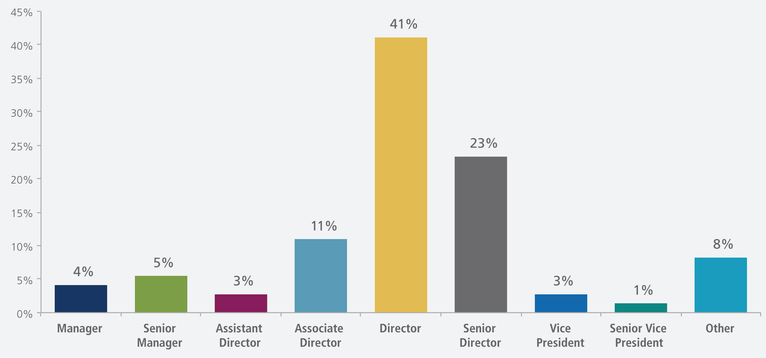
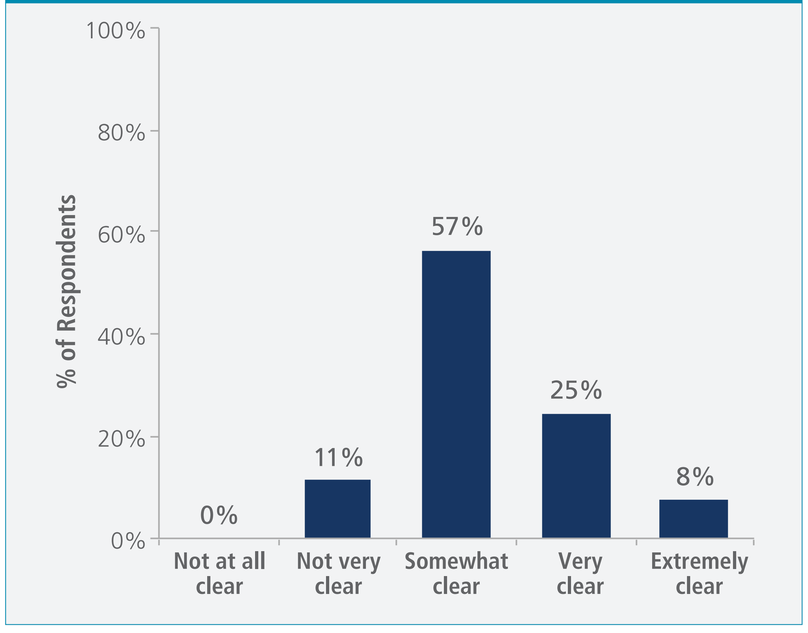


Figure 2. Current Title in Organization



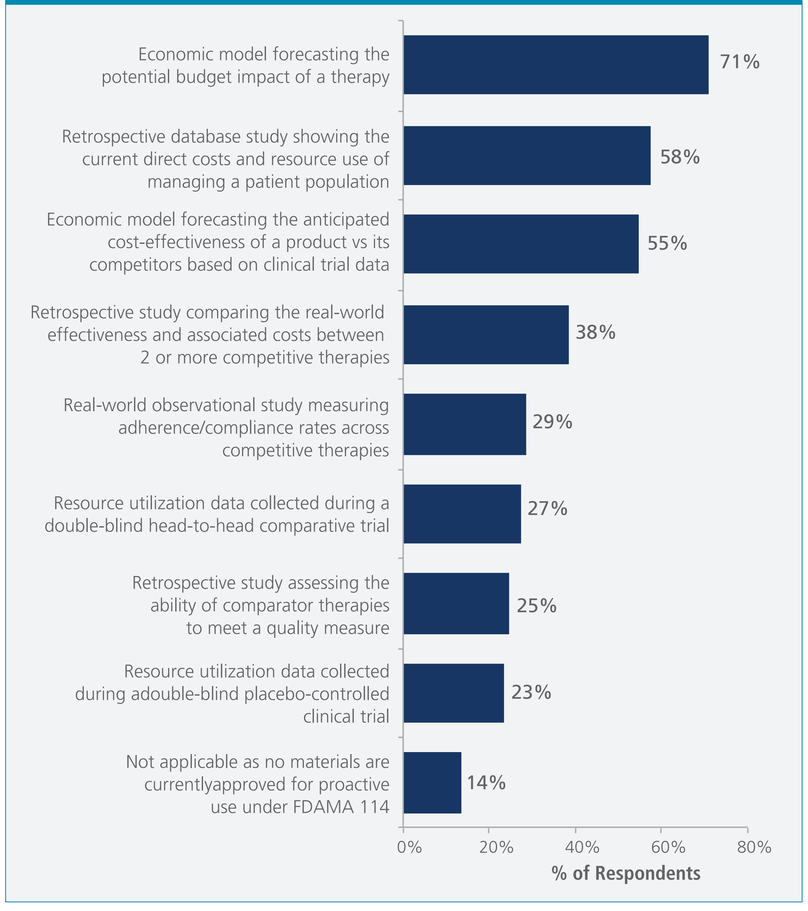
- A majority of respondents (73%) indicated that their organization has a specific process for approval of FDAMA 114 materials, with 21% noting that a process is currently under development and 7% reporting that their organization does not have plans to develop a specific process over the next 12 months.
- Of those with an approval process in place, most rated that process as somewhat or not very clear (**Figure 3**).

Figure 3. Clarity of Approval Process



- From the time of materials submission, the typical duration of review for FDAMA 114 materials was 1 to 3 months (57%), with some respondents reporting shorter timelines (2 to 3 weeks, 21%) and others requiring over 3 months to gain approval (4 to 6 months, 15%; 7 to 12 months, 8%).
- Legal and regulatory (both 88%) were the most common departments required to provide final approval of FDAMA 114 materials followed by medical (62%), HEOR (60%), and other (11%).
- Many respondents (41%) found gaining approval of HCEI materials under FDAMA 114 to be very or extremely difficult and largely noted that decisions were somewhat (56%), not very (15%), or not at all (7%) consistent across brands, with similar consistency reported within brands.
- Nearly all respondents (96%) identified payers as an eligible audience for FDAMA 114 materials, followed by integrated delivery networks (63%), accountable care organizations (58%), healthcare providers with financial responsibility for the patient (23%), organizations that develop value frameworks (23%), other (15%), healthcare providers (in general) (11%), patient advocacy groups (8%), and research societies (5%).
- A variety of types of HCEI is approved by manufacturers for proactive use. As seen in **Figure 4**, economic models forecasting the potential budget impact of a therapy, was the most common and resource utilization in double-blind placebo controlled trials was the least common.

Figure 4. Types of HCEI Approved for Proactive Use Under FDAMA114



- Overall, only 17% of respondents agreed very much (16%) or completely (1%) that their organization utilizes FDAMA 114 effectively to support product value, with most manufacturer respondents noting that they only agree somewhat (40%), not very much (29%), or not at all (14%).
- Most problematic to manufacturers were the FDAMA 114 terms "competent and reliable scientific evidence" and "directly relates to an approved indication," which have very much or extremely limited the ability to convey HCEI according to 36 and 41% of respondents, respectively. The terms "formulary committee or other similar entity" and "health care economic information" also very much or extremely limited manufacturers' ability to convey HCEI according to 23% and 27% of respondents, respectively.
- With regard to the changes proposed in a March 2016 AMCP Partnership Forum to add clarity to FDAMA 114 (**Table 1**), the majority (62 to 84%) very much or completely agreed that the suggested changes would be helpful in improving their organization's ability to effectively communicate HCEI. Note that the 21st Century Cures Act enacted in December 2016, after the collection of this survey data, implemented changes to the original FDAMA 114 language to add clarity, some of which were in alignment with AMCP recommendations.

Table 1. Proposed Changes to FDAMA 114 Language

FDAMA 114 Language	AMCP Partnership Forum Proposed Changes
"Competent and reliable scientific evidence"	"Truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate and valid."
"Formulary or other similar entity"	"Health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."
"Health care economic information"	"Any analysis that identifies, measures, or compares the economic, clinical or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."
"Directly relates to an approved indication"	"Information about a product that may vary from the parameters utilized in a randomized controlled trial, such as dosage forms, settings, or populations studied, as long as it is still used within the approved disease indication."

CONCLUSIONS

- While the use of FDAMA 114 has been limited over the past 20 years, the evolving value-driven healthcare environment and recent legislative updates have spawned renewed interest in the exchange of HCEI.[2]
- Unclear processes, inconsistent approval of materials, and former legislative terms have substantially impacted the exchange of HCEI under FDAMA 114, according to manufacturer stakeholders.
- Recent approval of 21st Century Cures and the January 2017 FDA guidance provided some clarity and may improve the effective exchange of HCEI among payers and manufacturers, but to what extent is unclear. The content and impact of the finalization of FDA's guidance, expected this fall, is also uncertain. Regardless, this research reinforces that manufacturers need assistance and clarity on parameters for proactive research dissemination to payers and should be considered by the FDA when constructing their guidance.
- Additionally, given the recent updates, review of manufacturer's own policies and procedures is warranted.

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1. Neuman, PJ, et al. *Value Health*. 2015;18:682-689.
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