

21st Century Cures Initiative Proposals

I. Patient-Focused Drug Development

- **A Framework for Patient-Centric Drug Development** Advance the science of Patient Preference Assessment (PPA) by the creation of a public-private partnership (PPP) to develop methodologies for patient preference assessments and to conduct patient preference studies and establish a shared infrastructure to conduct patient preference studies on behalf of patient groups, researchers, and Sponsors. Issue guidance on how PPA data can be used to inform drug development and specific guidance for patient groups and researchers on best practices for establishing electronic patient registries, documenting natural histories, and qualifying patient reported outcome tools (PROs). Via the PPP, establish a framework for patient organizations to provide input to Sponsors and FDA at various stages of drug development for their condition in general on important aspects of the drug development program. Clarify FDA policy that Sponsor outreach to patient groups to better understand their perspectives on the design and conduct of a particular clinical development program does not constitute marketing of an unapproved investigational product subject to enforcement. Expand the use of Special Government Employees to solicit patient views during drug development. Explicitly link the statutory benefit/risk framework to patient perspectives and preferences.

II. Modernizing Clinical Trials and Drug Development

- **Biomarker and Surrogate Endpoint Acceptance and Qualification:** Create a more predictable, transparent, and scientifically sound process for qualifying biomarkers for general drug development and for accepting biomarkers, surrogate markers, and alternative endpoints for use within individual drug development programs. Restructure FDA's Biomarker Qualification process into a pilot program that leverages external scientific expertise to develop consensus for biomarker, surrogate marker, and alternative endpoint qualification, with associated timelines for development and review.
- **Expediting the Development of Novel Therapies for Serious or Life-threatening Diseases:** Building on their success, further strengthen and expand existing programs. Clarify that products for which surrogate endpoints are used are eligible for Breakthrough Therapy designation, better leverage real-world data to confirm clinical safety and effectiveness in the post-market, and support the ADAPT Act to expedite approval based on targeted/limited population studies.
- **Harnessing "Big Data" and Real-World Evidence to Advance the Development of 21st Century Cures:** Facilitate researcher access to government data sources under responsible patient privacy, security, and confidentiality safeguards. Develop a private-public partnership to develop, validate, and pilot methodologies for interrogating electronic health records and



other real-world data sources to assess medical outcomes and support claims of safety and effectiveness. Establish an approval mechanism for therapies intended to treat serious conditions, based on clinical evidence that indicates a drug may demonstrate substantial improvement over existing therapy and has a positive benefit-risk profile for its intended use, followed by monitoring of safety and effectiveness through the collection of real-world data.

- **Improving Patient Access to Experimental Therapies through Effective Expanded Access Processes:** Require enhancements in FDA education and communication. Encourage and help facilitate the establishment of expanded access programs in early drug development for companies that are small businesses and whose drug is designated as a Breakthrough Therapy. Establish a clear and structured approach for FDA consideration of data and information from expanded-access use.

III. Focused Innovation on Unmet Medical Needs

- **Longitudinal Study to Identify Genetic and Other Predictors, Precursors, & Signs of Alzheimer’s and Other Diseases:** Develop and execute a large-scale, longitudinal study that will include sequencing the genomes and obtaining biological samples from individuals in age cohorts through age 90 that may predict Alzheimer’s Disease (AD) or other chronic diseases for which the cause is unknown or poorly understood.
- **Incentives for R&D of Antibiotics, Novel Treatments, Vaccines, and Biological Approaches to Combat Antimicrobial Resistance:** To try to deal with the formidable economic and regulatory challenges in discovery, development, and delivery of these kinds of products, specifically those related to an increasing array of antibiotic-resistant pathogens, establish greater incentives for development of targeted infectious disease products.
- **Encouraging Innovation:** Consider ways to enhance current incentives to spur further innovation and scientific advancement in drug development, in particular, the concept of regulatory exclusivity.

IV. Promoting Scientific and Medical Dialogue

- **Improving Scientific and Medical Dialogue to Enhance Patient Care:** Improve the medical and scientific dialogue on the most effective patient care by removing certain limitations on the ability of biopharmaceutical manufacturers to communicate with health care professionals and payor representatives concerning truthful and not misleading information about approved uses or medically accepted alternative uses of approved products.



V. **Preparing FDA for the Future**

- **FDA Scientific Infrastructure, Management, and Human Capital:** Improve FDA access to adequate funding & resources, promote the Agency's ability to attract and retain scientific and technical experts, and enhance FDA's institutional management processes and expertise. Specifically, grant FDA additional flexibility to provide competitive compensation to recruit highly qualified staff; provide new FDA management tools, including an external Management Review Board; and provide greater access to external expertise through Special Government Employees and Advisory Committees.

VI. **Delivery of Innovative Therapies**

- **Delivery-Side Proposals:** Ensure a robust reimbursement environment that continues to encourage innovation. This includes, but is not limited to examining patient cost sharing issues in Part D, new technology add-on payments, Medicare beneficiary appeals process and coding issues.



Biopharma answers the call for cures

By Jim Greenwood

How can we give patients faster access to innovative treatments and cures? That's the question being asked of our nation's foremost medical experts and innovators by members of the House of Representatives' Energy and Commerce Committee through an initiative called "21st Century Cures."

Alzheimer's is one area that represents a tsunami of public health challenges confronting us, and therefore must rise to the top of this timely discussion. Without intervention or prevention to delay or slow Alzheimer's progression in patients, or the discovery of a cure, the disease will overwhelm the healthcare system within the next 25-30 years.

An estimated 24 million people worldwide have dementia, most from Alzheimer's disease. That number is predicted to double by 2020 – just over five years from now – and triple by 2040. The numbers are equally striking for the U.S., where more than a million people over the age of 65 are afflicted today – a number that is expected to triple by 2050.

The financial cost to the U.S. healthcare system of caring for individuals with the disease is estimated at over \$200 billion today and will rise to over \$1 trillion by 2050.

The societal costs are inestimable. These predictions do not include individuals with early-onset of the disease, who are under the age of 65 at first onset or diagnosis.

Something must be done.

I believe there are three key steps that will help expedite the development of cures and treatments:

1. **Collaborate** by forming public-private partnerships and coordinating efforts with existing initiatives;
2. **Collect** health care data, genomic data, and biospecimens to identify potential risk factors, causes, biomarkers and targets for intervention; and
3. **Communicate** the outcomes of the study publicly to translate the results into treatments and, potentially, a cure.

I propose the development and execution of a large-scale, longitudinal study to sequence the genomes of 100,000 volunteers in age cohorts from those in their 20s through those in their 80s, obtain biospecimens and additional health care data from those individuals, and develop biological markers that may predict Alzheimer's or other chronic diseases for which the cause is unknown or poorly understood.



This large-scale, long-range study will not only yield data necessary to find ways to cure and prevent Alzheimer's, it would help researchers find ways to treat hundreds of other diseases for which we still lack adequate therapies.

There is broad agreement that advancements in biologic and drug development will best be accomplished through collaborations that bring together knowledge, skills, and expertise, as well as funding, from the public and private sectors.

Public and private entities worldwide are engaged in efforts to understand the disease, to determine how best to develop therapies, and to address the enormous challenges facing caregivers. Such partnerships and consortia already are making progress in a number of areas with high public health impact, including Alzheimer's.

These multiple efforts need to be coordinated effectively for the greatest possibility of realizing a return on investment that expedites prevention of the impending Alzheimer's crisis.

It is well recognized that a first step toward a cure is to identify the cause of the disease, individuals who are at risk for the disease, and potential targets for intervention.

Our hopes for cures hinge on understanding how to intervene to halt the disease's progress. Through this proposed study, we would identify precursors and early signs of disease or disease risk. This information could be made publicly available so drug and device developers would have defined targets and potentially could develop ways to prevent and treat the disease.

The urgency of finding a cure for Alzheimer's cannot be overstated. It is difficult to find anyone whose life has not been affected by this devastating disease. Biotech holds the greatest promise for finding a cure. We must act now for the patients and their families who are counting on us.

Greenwood is president and CEO of the Biotechnology Industry Organization.

A Framework for Patient-Centric Drug Development

I. SUMMARY

The future of 21st century drug development will require active collaboration and cooperation among FDA, drug sponsors, and most importantly patients to better understand patient perspectives on benefit/risk determinations and meaningful clinical outcomes. Methods for soliciting the views of patients, as well as their caregivers and healthcare providers, should be further evolved into data driven mechanisms for conveying patient preferences during the drug development process.

Specifically, this paper proposes to:

I. Advance the Science of Patient Preference Assessment

- Create a public-private partnership (PPP) to develop methodologies, survey tools, and related data collection methods for patient preferences assessments. Establish a shared infrastructure to conduct patient preference studies on behalf of patient groups, researchers, and Sponsors.
- Issue FDA guidance on how patient preference assessment data can be used to inform drug development and specific guidance for patient groups and researchers on best practices for establishing electronic patient registries, documenting natural histories, and qualifying patient reported outcome tools (PROs).

II. Establish a Framework for Patient Engagement during Drug Development:

- Based on recommendations from the private-public partnership, establish a framework for patient organizations to provide input to sponsors and FDA at various stages of drug development for their condition in general on certain important aspects, including benefit/risk, unmet medical needs, study protocols, meaningful endpoints and clinical outcomes, enrollment strategies, natural histories, novel tools and methodologies, and alternative study designs.
- Clarify FDA policy that Sponsor outreach to patient groups to better understand their perspectives on the design and conduct of a particular clinical development program does not constitute marketing of an unapproved investigational product subject to enforcement. Describe the appropriate parameters and regulatory/legal safe-harbor for Sponsor engagement with patient groups during drug development.
- Expand the use of Special Government Employees to solicit patient views during drug development
- Explicitly link the statutory benefit/risk framework to patient perspectives and preferences.

II. BACKGROUND

While FDA's statutory standards for approving a new drug is on the basis of safety and effectiveness, modern drug development in practice is the process of carefully assessing the benefits and risks of a product in the context of unmet medical need, disease severity, and the body of scientific evidence. Fundamental to that careful assessment is the patient view on benefit/risk and meaningful medical outcomes. Historically, most patient organizations have not played an active role in providing input on drug development programs and FDA and sponsors have made key drug development decisions with varying degrees of patient input. However, it is widely recognized that this model has become outdated.

Patient views on benefit-risk can be sophisticated and nuanced.ⁱ Depending on the context of the disease severity, progression, and available therapeutic options, patients may express a higher threshold for tolerating potential risks or scientific uncertainty in exchange for meaningful clinical benefit. Such patient feedback should be captured in a data-driven, systematic process to help inform the drug development and FDA review process.

As FDA recently stated:

*Assessment of a product's benefits and risks involves an analysis of the severity of the condition treated and the current treatment options available for the given disease. This information is a critical aspect of FDA's decision-making as it establishes the context in which the regulatory decision is made. FDA believes that drug development and FDA's review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and current available options in a therapeutic area.*ⁱⁱ

To address that need for a structured approach to capturing patient perspectives, recent initiatives, such as the PDUFA V Patient-Focused Drug Development Program (PFDD), have begun to implement mechanisms for elevating the patient voice in the drug development and FDA review processes. This program has supported a series of 20 public workshops to solicit patient views on benefit/risk, which is then communicated through the "Voice of the Patient" reports.^{iii,iv}

FDA has also relied on other mechanisms to solicit patient perspectives, such as engaging patient representative and external experts as Special Government Employees to seek patient input on individual development programs under appropriate confidentiality agreements. Additionally, FDA's Advisory Committees typically include a consumer representative, a patient group representative, or both, charged with representing the consumer and/or patient perspectives on issues and actions before the advisory committee; serving as a liaison between the committee and interested consumers, associations, coalitions, and consumer organizations; and facilitating dialogue with the advisory committees on scientific issues that affect consumers.^v

It is critical that the information, feedback, and data collected by patient constituencies are used to inform FDA regulatory decision-making, particularly when the benefits and risks of an individual product are being carefully weighed and evaluated. CDER and CBER's Structured Benefit Risk Framework plays an important role in transparently assessing and communicating how reviewers weighed a product's benefits and risks so that FDA staff and external stakeholders can understand how any potential benefit/risk

value judgments were incorporated into the broader decision based upon the body of scientific evidence.^{vi}

FDA's Center for Devices and Radiological Health (CDRH) has also been influential in the evolution of a systematic benefit/risk framework through the issuance of the March 2012 guidance *Factors to Consider when Making Benefit-Risk Determination in Medical Device Premarket Approval and De Novo Classifications*. The guidance explicitly outlines the key considerations around the assessment of benefits and risks in the context of the body of scientific evidence to help guide reviewer decision-making.^{vii} As noted in the guidance, "By documenting reviewers' thought processes as part of the administrative record and, in certain cases, the publicly available summary of our decision, sponsors will have a better idea of the basis for FDA's favorable decisions and gain a greater understanding of what factors were considered as part of an approval..."

III. PROBLEM STATEMENT

While PDUFA V has made major strides in elevating the patient voice in the FDA review process, these mechanisms often are not linked to individual development programs or seek input at the end of the development process. Additionally, there is a lack of survey tools and methodologies for assessing patient preferences in a manner that efficiently produces high quality data. Patient feedback has been anecdotal and periodic. A more systematic, data driven approach to quantifying patient preferences is needed.

A new, evolved framework is required to solicit patient views throughout the drug development process in a manner that is systematic, data driven, and methodologically robust. This patient preference data can help ensure that clinical trials are designed to be practical and patient-friendly, that the endpoints developed and studied are meaningful to patients with the disease, and that regulatory approval decisions are grounded in patient perspectives on benefits and risks.

As Benefit/Risk and PFDD continue to evolve, the following four themes should be addressed.

- *Getting beyond the 20 disease states (the WHO?):* While the initial foray by the FDA into the PFDD by focusing on 20 disease states has been a good start, it is time to enhance the utility of PFDD. Immense interest from patient groups (over 4,500 comments were submitted to the docket, addressing over 90 disease areas) in addition to the FDA timetable for incorporating the benefit/risk framework into reviews dictate that we not only improve on the 20 disease states, but establish a clear path for patient organizations to engage the agency more broadly in a systematic and dynamic manner.
- *Data Collection (the WHAT?):* Getting feedback from a large, targeted and representative cohort can provide much more value than feedback during a public meeting or an open docket. Since the Agency is neither positioned nor resourced to collect this data directly from patient constituencies, external organizations are better prepared to develop this information to submit to FDA. A roadmap from the Agency is needed as to what data the review divisions would find useful and actionable.

- *Setting the groundwork for data collection/surveys (the HOW?):* Continuous patient education is needed to develop meaningful data and not just approach the Agency with anecdotal accounts. To accomplish this, useful and cost-effective data collection/analysis instruments are needed to aid patient advocacy groups. Development of such instruments should be informed by the needs articulated by the agency. Several different patient groups have already commissioned surveys and transmitted their findings back to the agency – including patient groups for the following disease states: lung cancer, chronic fatigue syndrome, Duchenne muscular dystrophy, and narcolepsy. Current data collection efforts have been mixed, and it is unknown how the Agency will utilize the collected information. Without a robust and representative data set, this entire effort could risk becoming a missed opportunity.
- *Output from patient engagement (the WHY?):* Most importantly, we need to understand how the data collected, whether through surveys, meetings, dockets, is going to affect the FDA's benefit/risk frameworks in drug reviews. Other than the "Voice of the Patient" report, it is largely unknown what, if anything, the agency is learning from these meetings. Clear guidelines are lacking on how the agency will collect information (from public meetings, dockets, and perhaps surveys), how the review division will utilize this information at the reviewer level, and how this will be systematically implemented across the agency.

IV. PROPOSALS

PART I: ADVANCE THE SCIENCE OF PATIENT PREFERENCE ASSESSMENT:

1. Public-Private Partnership to Promote Patient Benefit/Risk Assessment:

Create a public-private partnership (PPP) to develop methodologies and study protocols, as well as conduct studies to assess patient preferences. The PPP would develop methodologies and recommendations for a framework for use by patient organizations. This would help evolve the PFDD from a process characterized by anecdotal information about patient experience provided without clear use and impact to a sustainable system for systematically capturing and incorporating patient voices on certain important aspects of drug development, including benefit/risk, unmet medical needs, study protocols, meaningful endpoints and clinical outcomes, natural histories, novel tools and methodologies, and alternative study designs.

- *Evolve the Methods and Tools for Patient Preference Assessments:* The partnership would engage with academia, government, patient groups, and Sponsors to catalogue and further develop the scientific methodologies, survey tools, and supporting information technologies for conducting patient preference studies in a manner that is robust, validated, and scalable across multiple therapeutic areas.
- *Establish a Shared Infrastructure to Conduct Patient Preference Assessments:* The program's results would serve regulatory, patient, sponsor, payer, and physician purposes. This body would be able to pool funds from multiple stakeholders to conduct larger scale and higher quality preference studies than can reasonably be conducted by a single sponsor or patient advocacy group. With the use of world-class experts to help design, conduct, and analyze the results, many of the limitations of currently conducted preference studies could

be overcome. These studies also could be integrated into new versions of PFDD meetings that make use of structured data in the preparation for and conduct of the meetings.

- *Evolution of the PFDD Meetings Process:* The PPP could work with patient advocacy groups with experience in benefit-risk (e.g., National Health Council, FasterCures) to develop a draft guidance for FDA consideration regarding how patient-focused drug development meetings run by patient organizations or other external groups can be conducted most effectively and what deliverables should be expected from them. Precedent in this area includes the Parent Partner Muscular Dystrophy draft guidance on clinical trials for Duchenne Muscular Dystrophy. Since the meetings will be run by non-FDA organizations, there is the opportunity to extend and improve the meetings in a fashion that is not possible for the FDA, such as incorporating structured data gathering before the meeting and using those results within the meeting.

The overarching goal of this public/private partnership would be to move away from the public meetings as a primary source of patient input to a standardized, repeatable, and representative pre-competitive data collection model that could be used across FDA divisions. The data would be viewed as representative and incorporated into the B/R framework in a visible way and actively considered by FDA reviewers in the overall regulatory decision making process. The three main components of the pilot would be:

- A. *Expertise and recommendations on the best methods/science of patient engagement:*
 - Best practices for Sponsor and FDA engagement with patient group (and health care providers where appropriate). Identification of relevant data most important to both the agency and the patient groups
 - Types of market research/focus group data that sponsors collect can be used in submissions
 - Catalogue of available patient preference data/methodologies and recommendations/improvements to current data or methodologies
 - Attributes and characteristics of high-quality patient data
- B. *Develop a repository of the best technology to capture, analyze and store patient input:*
 - Best means to collect patient data and optimal survey/data collection instruments
 - Development of data/methods collection small patient groups may utilize independently
 - FDA use of large existing patient data sets (e.g. from PatientsLikeMe)
- C. *Translating the methods:*
 - Analysis, interpretation and communication of the data
 - Application of these methods to inform benefit/risk framework that would be initially established in clinical development and updated throughout the product lifecycle into the postmarketing space
 - Optimal uses of the data, scientific limitations, and biases of such methodologies
 - Best practices for patient groups and FDA engagement throughout drug development and evaluation.

- Updating benefit/risk framework to reflect the evolution of the product's benefit/risk profile across its lifecycle

2. Linking Patient Preference Data to Regulatory Decision-Making: The PPP would also issue recommendations to FDA on best practices for conducting patient preference studies to help guide regulatory decision making. Based on those recommendations, FDA will issue guidance on best practices for patient preference studies, the process and timeframe for submitting that data, and how the data resulting from the studies will be used to inform individual product development programs and FDA's marketing approval decisions.

To provide guidance to patient groups who choose to collect data from their constituencies to advance patient-centric drug development, require that FDA issue guidance within 2 years directed specifically towards patient advocates and related researchers for on best practices for establishing electronic patient registries, documenting natural histories, and qualifying patient reported outcome tools (PROs).

PART II: ESTABLISH A FRAMEWORK FOR PATIENT ENGAGEMENT DURING DRUG DEVELOPMENT:

3. Framework for Patient Engagement during Drug Development: Based upon recommendations from the public-private partnership, establish a formalized framework for patient organizations to provide input to sponsors and FDA at various stages of drug development for their condition in general and on clinical trial design and operation. This may include the use of Special Government Employees (see below).

The recommendations for this framework would build upon similar work already being conducted by the National Health Council, FasterCures, and the Medical Device Innovation Consortium.^{viii,ix} Such a framework could help facilitate patient involvement earlier in drug development to inform key decision about a particular development program, such as more effective study recruitment and enrollment strategies, the development of surrogate or intermediate clinical endpoints, and the establishment of qualified patient-reported outcomes.

FDA should continue to rely on mechanisms for accessing external patient perspectives during the FDA review phase, while integrating a revised framework for systematically integrating patient views into the development process. Appropriate safeguards would be established to protect confidential commercial information and intellectual property prior to FDA approval.

4. Clarify Federal Policy on Patient Engagement: Clarify FDA policy that Sponsor outreach to patient groups to better understand their perspectives on the design and conduct of a particular clinical development program does not constitute promotion or marketing of an unapproved investigational product or indication subject to enforcement. Further, FDA should issue guidance describing the appropriate parameters and regulatory/legal safe-harbor for Sponsor engagement with patient groups during drug development.

5. Expand the Use of Special Government Employees to Solicit Patient Views during Drug Development: Use Consultation with External Experts on Rare Diseases, Targeted Therapies law as a model to amend Patient Participation in Medical Discussions Provision in FDASIA §903.

Proposal: The following amendments to FDCA Sec. 569 (21 U.S.C. 360bbb), should be considered (blue/underlined):

"The FDA shall develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by:

- Fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and
- Exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry.

For new drugs and biological products designed to treat serious or life-threatening diseases or address an unmet medical need, the following process may be utilized:

- Consultation with Medical Experts and Patient Advocates: Sponsors may request and FDA will grant an in-person patient perspective benefit-risk meeting with FDA.
- Consultation with External Experts: The meeting could include:
 - Medical and scientific experts identified by the Sponsor
 - Patient advocates identified by the Sponsor
 - Senior FDA staff from review team
 - External medical, scientific, and patient advocacy experts identified by FDA (Allow for use of Special Government Employees to protect intellectual property)
- Meeting could take place prior to conducting any clinical trial during drug development (Phase 1, 2, or 3)
- Topics for Consultation: Topics for consultation may include:
 - Severity of disease
 - The unmet medical need associated with disease
 - The willingness and ability of individuals with disease to participate in clinical trials
 - Assessment of the benefits and risks of therapies to treat disease
 - The general design of clinical trials for disease population and subpopulations
 - The demographics and the clinical description of patient populations
- Any areas of significant disagreement between FDA and meeting participants will be documented in the meeting minutes.

In accordance with current law, appropriate safeguards would be implemented to protect confidential commercial information and intellectual property prior to FDA approval.

6. Explicitly Link the Statutory Benefit/Risk Framework to Patient Preferences:

Under FDASIA, Congress amended Section 505(d)(7) of the Federal Food Drug and Cosmetics Act to direct FDA to implement a structured Benefit/Risk Framework. However, there is no explicit linkage between the benefit/risk framework and the information collected from patients as part of the PFDD program. Consequently, it is unclear how the data collected from the 20 meetings and patient preference studies will be used to inform the conduct of clinical development programs and individual product approval decisions.

Proposal: Amend Section 505(d)(7) as follows:

"The Secretary shall implement a structured benefit-risk assessment framework in the new drug approval process to facilitate the balance consideration of benefits and risk, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs. [The Secretary shall incorporate patient perspectives into the benefit-risk assessment that take into consideration severity of disease or condition, differing tolerances for patients suffering from differing severities of a condition, and improvements to quality of life for patients.](#)"

Non-Statutory Legislative Language:

[To accomplish the amendments by this Act to Section 505\(d\)\(7\) of the FDCA, FDA shall work with NIH, AHRO, public-private partnerships, industry, medical researchers, health information technology experts, and patient advocacy organizations to inform the publication of guidance on methodologies and criteria for collection of patient centric risk/benefit data for inclusion in benefit-risk assessments. This effort shall include analysis of the current patient preference studies and related data sources available and being collected as well as how that information could be utilized to inform this process. The guidance shall be published within 2 years.](#)

REFERENCES:

ⁱ National Health Council, Statement for the Record, 21st Century Cures Initiative Hearing, July 11, 2014, www.nationalhealthcouncil.org/NHC_Files/Pdf_Files/NHC-21stCenturyCuresInitiative-Patient_Engagement.pdf

ⁱⁱ FDA, *Enhancing Benefit-Risk Assessment in Regulatory Decision-Making*, <http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm326192.htm>

ⁱⁱⁱ FDA, *Patient Focused Drug Development Consultation Meetings*, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm349457.htm>

^{iv} FDA, *The Voice of the Patient: A Series of Reports from FDA's Patient Focused Drug Development Initiative*, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm>

^v FDA, *Consumer Representatives*, <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/ucm231782.htm>

^{vi} FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making: Fiscal Years 2013-2017*, February 2013, <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>

^{vii} FDA, *Factors to Consider when Making Benefit-Risk Determination in Medical Device Premarket Approval and De Novo Classifications*, March 2012

Factors FDA Considers in Making Benefit-Risk Determinations

- A. Assessment of the Benefits of Devices
 - a. The type of benefit(s)
 - b. The magnitude of benefit(s)
 - c. The probability of the patient experiences one or more benefit(s)
 - d. The duration of effect(s)
- B. Assessment of the Risks of Devices
 - a. Severity, types, number and rates of harmful effects associated with the use of the device
 - i. Device-related serious adverse events
 - ii. Device-related non-serious adverse events
 - iii. Procedure-related complications
 - b. Probability of harmful event
 - c. Duration of harmful event
 - d. Risk from false-positive or false negative results for diagnostics
- C. Additional factors in the Assessment of the Probable Benefits and Risks of Devices
 - a. Uncertainty
 - b. Characterization of the Disease
 - c. Patient tolerance for risk and perspective on benefit
 - d. Availability of alternative treatments or diagnostics
 - e. Risk mitigation
 - f. Post-market data
 - g. Novel technology addressing unmet medical need

^{viii} Medical Device Innovation Consortium, *Patient Centered Benefit-Risk Assessments (PCBR)*, <http://mdic.org/projects/pcbr/>

^{ix} National Health Council, Statement for the Record, 21st Century Cures Initiative Hearing, July 11, 2014, www.nationalhealthcouncil.org/NHC_Files/Pdf_Files/NHC-21stCenturyCuresInitiative-Patient_Engagement.pdf

Biomarker and Surrogate Endpoint Acceptance and Qualification

I. SUMMARY

Create a more predictable, transparent, and scientifically sound process for qualifying biomarkers for general drug development and for accepting biomarkers, surrogate biomarkers and alternative endpoints for use within individual drug development programs. Restructure the Food and Drug Administration's (FDA) public Biomarker Qualification process into a pilot program that empowers industry and FDA to leverage external scientific expertise to concurrently and transparently develop scientific and regulatory consensus for biomarker, surrogate biomarkers and alternative endpoint qualification, with associated timelines for development and review.

II. BACKGROUND

Biomarkers are often integrated into drug development in the context of an individual Investigational New Drug Application (IND), New Drug Application (NDA), Biologics License Application (BLA), or labeling update to support patient stratification, enrichment/patient selection, co-development of a diagnostic test, or as surrogate endpoints to predict clinical benefit. In this scenario, biomarkers become accepted in the context of the specific drug through its regulatory review process and, generally, will only be useful in the context of that specific drug program. There is little transparency or predictability in this process; Sponsors do not have the ability to leverage external scientific, technical, and/or medical expertise; and there are no review timelines associated with biomarker or alternative endpoint review. Also, in order to use these biomarkers for new regulatory submissions, they must be justified each time with the relevant review divisions, often requiring additional data specific to the new drug development program.

Industry and regulators have recognized that there is an opportunity to realize additional efficiency in the evaluation and employment of biomarkers *across* drug development programs. Historically, FDA began its public biomarker qualification process as a pilot program from 2006-2008,¹ then developed a formal, Center for Drug Evaluation and Research (CDER)-housed regulatory biomarker qualification process in 2009.² This

¹ Goodsaid FM, Frueh FW, and Mattes W. (2008) Strategic paths for biomarker qualification. *Toxicology* 245(3): 219-23.

² Woodcock J, Buckman S, Goodsaid F, Walton MK, and Zineh I. (2011) Qualifying biomarkers for use in drug development: a US Food and Drug Administration overview. *Expert Opin Med Diagn* 5(5):369-74.



process is supported by a Draft Guidance for the Qualification of Drug Development Tools, published in 2010 and finalized in 2014.³

FDA defines *biomarker qualification* as “a conclusion that within the stated context of use, the results of assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review.” Once qualified for a specific context of use, therefore, a biomarker can be used by drug developers without re-review. The FDA public Biomarker Qualification Program is intended for biomarkers that will be used in multiple drug development programs, and consortia or collaborative groups are likely to be the primary source of biomarkers for qualification. However, with additional safeguards to protect confidential information, a re-structured Biomarker Qualification Program could be utilized by Sponsors of individual drug development programs who decide that the additional transparency, access to external expertise, and review timelines would allow them to more efficiently qualify a biomarker or surrogate endpoint for a restricted context of use (*i.e.*, within a specific product development program).

Essential to the Biomarker Qualification Program, as well as the acceptance of biomarkers through individual drug development programs, is an understanding of *context of use*, defined by FDA as, “a comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker.” The context of use statement describes all important criteria regarding the circumstances under which the biomarker is qualified and defines the boundaries within which the available data adequately justify use of the biomarker. Most importantly, the context of use also determines the type and magnitude of data required for regulatory acceptance or qualification of the biomarker or surrogate endpoint.

III. PROBLEM STATEMENT

There are significant challenges for Sponsors of individual drug development programs seeking to utilize biomarkers, surrogate biomarkers and, particularly, alternative endpoints *within* their specific drug development programs. In particular, the process through which advice/consultation can be sought from additional FDA offices and staff (*i.e.*, Office of Translational Sciences, Study Endpoints and Labeling Development staff, *etc.*) to augment the experience/expertise of the FDA review divisions is not transparent. Additionally, there are no associated timelines for receiving input or decisions from those support offices or staff. Finally, there is no mechanism through which external scientific expertise can be leveraged, and this is exacerbated by difficulties hiring and retaining dedicated subject matter expertise within FDA.

³ FDA Guidance for Industry: *Qualification of Drug Development Tools* (2010). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>



The current FDA Biomarker Qualification Program that supports regulatory qualification of biomarkers **across** drug development programs also presents significant challenges. Chiefly, there are no timelines or responsiveness requirements, creating unpredictability for biomarker sponsors. Also, rather than prospective evidentiary standards, the program relies upon a Consultation and Advice stage that is designed to align FDA and submitters on *the standards for qualification to be used in each qualification submission (i.e., achieve regulatory consensus)*.⁴ The transit time through the Consultation and Advice stage of the process is long, and the outcomes from this stage are unpredictable. Qualification submissions since the inception of this process have been challenged to move beyond this stage, and this stage often re-evaluates (and contradicts) scientific consensus previously achieved through external scientific expertise and collaboration. Specifically, as of 2013, FDA had received 23 submissions to the Biomarker Qualification Program, with only three of those submissions receiving regulatory qualification. More concerning, though, is the fact that nearly 60% of those submissions (13) are mired in the Consultation and Advice stage of the Biomarker Qualification process, unable to align scientific consensus with regulatory consensus for qualification.⁵

While these challenges are important, the overarching problem central to both processes is the lack of prospective evidentiary standards for biomarker acceptance or qualification. Without guiding, prospective evidentiary standards tied to context of use, it is impossible to have a consistent, coherent view of biomarker acceptance or qualification, regardless of access to external expertise or review timelines. Once prospective evidentiary standards for biomarker acceptance or qualification have been developed, their employment with appropriate risk-benefit calculus can be monitored through a transparent process (*e.g.*, an Advisory Committee).

IV. PROPOSAL

Proposal 1 – Develop evidentiary standards for biomarker and surrogate endpoint acceptance/qualification

Engage the broader scientific and health care community to develop prospective evidentiary standards for regulatory acceptance/qualification of biomarkers and surrogate endpoints:

- FDA will engage stakeholders (including patients, industry, health care providers, academia, and government) and conduct [SPECIFIC NUMBER] workshops to develop scientific and regulatory consensus on prospective evidentiary standards

⁴ Goodsaid F. (2013) Impact of Biomarker Qualification Regulatory Processes on the Critical Path for Drug Development. *Biomarker Qualification* [Digital], Goodsaid and Mattes (Eds). Elsevier Press.

⁵ Amur S (2013) *Biomarker Qualification at CDER/FDA*. QIBA Annual Meeting, available online at: http://www2.rsna.org/re/QIBA_Annual_Meeting_2013/Index_files/PDF%20slides%20for%20posting%20Tuesday/3.%20AMUR.pdf



for acceptance or qualification of biomarkers for various contexts of use (including surrogate biomarkers and alternative endpoints)

- FDA will issue draft guidance for public comment on prospective evidentiary standards for acceptance or qualification of biomarkers for various contexts of use (including surrogate biomarkers and alternative endpoints), as well as criteria to be used to evaluate the robustness of those data, no later than [SPECIFIC NUMBER] months after passage.
- FDA will outline in guidance the expected contents of a briefing document for biomarker qualification whether it is for individual drug development program (Type B meeting) or for the review of a Biomarker Development Plan as submitted by a sponsor or consortium.
- FDA will finalize the guidance no later than [SPECIFIC NUMBER] months after the public comment period closes.

Proposal 2 - Improve the process for engaging FDA review teams to accept biomarkers, surrogate biomarkers and alternative endpoints, and modern approaches to clinical development within individual drug development programs

Create a more predictable, transparent, and scientifically sound process for accepting biomarkers, surrogate biomarkers, alternative endpoints, and modern approaches to clinical development within individual drug development programs:

- Individual Sponsors considering the use of a novel biomarker, surrogate biomarker, alternative endpoint, non-traditional clinical trial design, diagnostic, or other novel approach within a drug development program may, at their discretion, request a new Type B meeting (Biomarker and Endpoint Development Meeting) with FDA, optionally including external scientific expertise.⁶
- The participating Sponsor and FDA would coordinate to determine appropriate external scientific expertise to attend the meeting, in accordance with established guidelines on conflicts of interest and maintenance of confidentiality.^{7,8} The meeting could include, as appropriate:

⁶ FDA Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants* (2009), <http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf>

⁷ FDA Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: *Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees* (2008), <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf>

⁸ Regulation Certification for Special Government Employees (2002), <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048287.pdf>



- Medical and scientific experts identified by Sponsors
 - Senior FDA staff from the appropriate review division
 - Senior FDA staff from other review divisions as appropriate (*e.g.*, CDRH)
 - Representatives from FDA support offices/staff (*e.g.*, Study Endpoints and Labeling Development staff, Office of Translational Sciences, *etc.*)
 - External medical and scientific experts identified by FDA
- The goal of the Type B meeting would be for the Sponsor and FDA to reach agreement on the specific testing required for the proposed biomarker, surrogate biomarker, alternative endpoint, or use of novel approaches in the development of the product, guided by the prospective evidentiary standards published in guidance by the Agency.
 - Once development and data analysis are completed, FDA review, informed by external meeting attendees, would take place on a standardized timeline of [SPECIFIC NUMBER] days to promote a more predictable process.
 - If FDA rejects the proposed biomarker/surrogate endpoint/novel approach or rejects the data package submitted to fulfill a prior agreement through the Type B meeting, the agency would state clear rationale and identify any gaps in the Sponsor's submission.
 - FDA would report metrics associated with this program on a bi-annual basis to congress. These reports would include number and type of biomarkers and novel approaches (*e.g.*, surrogates for Accelerated Approval, safety, predictive, prognostic) as well as the number of review cycles necessary to reach agreement, and the number of markers subsequently used or abandoned as a result of this process.

Proposal 3 – Restructure FDA Biomarker Qualification Program

Enable external scientific expertise to be leveraged in biomarker and surrogate biomarker and alternative endpoint development, resulting in a process that would achieve parallel scientific and regulatory consensus for biomarker development with predictable timelines and outcomes of regulatory review:

- Consortia or Sponsors of individual development programs could engage FDA in a process that would initially result in an agreed Biomarker Development Plan (BDP), in which FDA, sponsor, and scientific experts would agree up-front on the context of use, evidentiary requirements, and data development plans to justify use of the biomarker prior to the initiation of large-scale data collection and analysis, guided by the prospective evidentiary standards published in guidance by the Agency.



- The agreed BDP would align the scientific consensus on biomarker development with clear expectations and evidentiary criteria necessary to support the use of a novel biomarker for regulatory purposes.⁹
- Engaging scientific expertise in parallel with regulatory expertise would facilitate a more informed discussion of the current and projected state of science, realistic/acceptable levels of residual uncertainty after qualification, and the appropriate evolution of qualification as additional evidence is generated.
- This Advisory Committee process would promote transparency (e.g. public release which includes: 1) description of data package assessed and 2) rationale for decision) and hold FDA accountable for any differences in determination of benefit-risk associated with fulfillment of the evidentiary standards for biomarker and surrogate endpoint qualification. Special consideration will be given to issues of confidentiality/disclosure for Sponsors or consortia seeking qualification of surrogate biomarkers or alternative endpoints with a context of use restricted to a specific drug development program.
- Under the BPD process¹⁰:
 - *Stage 1: Initiation*

Dedicated FDA Biomarker and Surrogate Endpoint Qualification staff, in consultation with appropriate reviewers from CDER Office of New Drugs (OND) will respond to the letter of intent under the agreed upon timeline of [SPECIFIC NUMBER] days.
 - *Stage 2: Consultation and Advice*

Relevant external scientific experts (potentially from NIH, academia/clinical practice, and industry) to the context of use (e.g. disease) would be convened under the auspices of an FDA Advisory Committee to establish the initial agreed BDP, guided by the prospective evidentiary standards published by the Agency, under the agreed upon timeline of [SPECIFIC NUMBER] days.¹¹
 - *Stage 3: Review of Full Qualification Package*

⁹ FDA Guidance for Industry: *Special Protocol Assessment* (2002), <http://www.fda.gov/downloads/Drugs/Guidances/ucm080571.pdf>

¹⁰ BDP Process is formatted to align with existing Biomarker Qualification Program as laid out in the Guidance for Industry and FDA Staff *on Qualification Process for Drug Development Tools* (2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

¹¹ FDA Guidance for the Public and FDA Staff: *Convening Advisory Committee Meetings* (2008), <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125651.pdf>

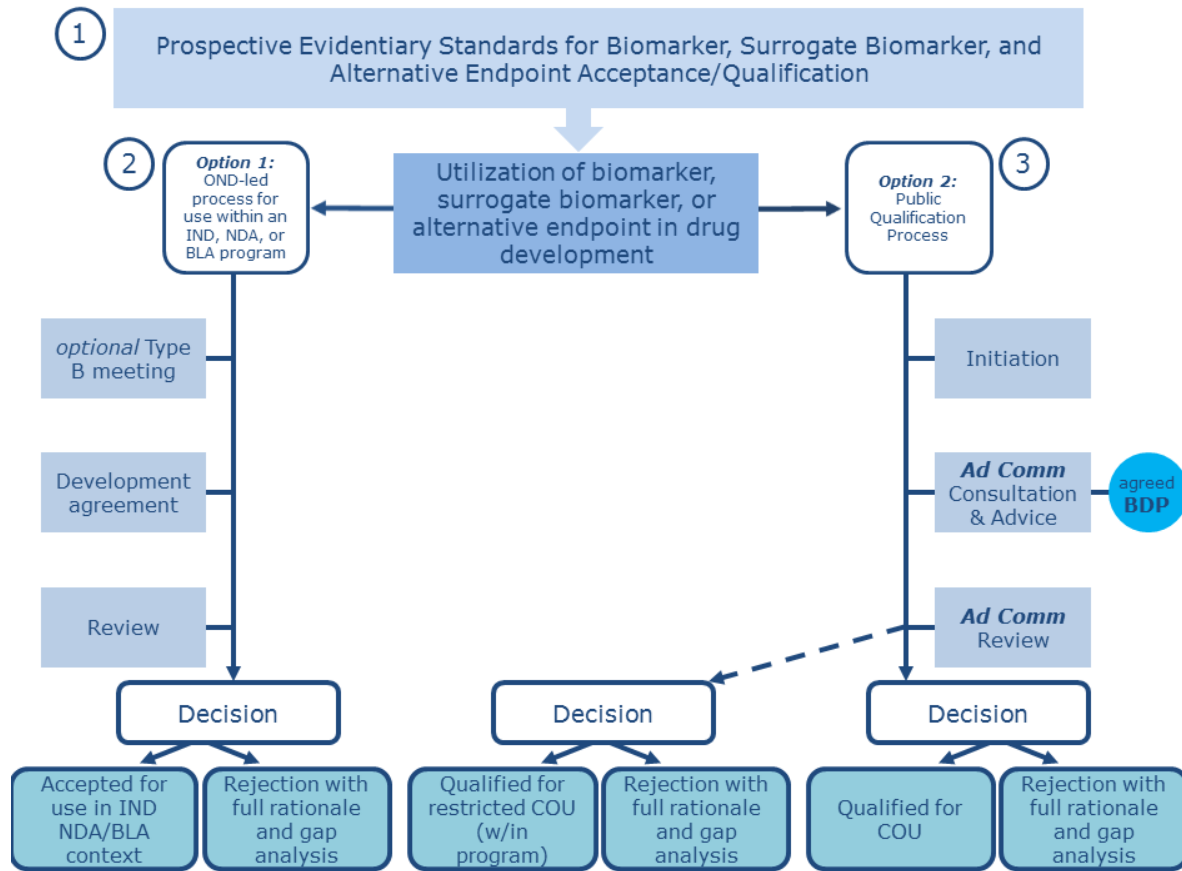


The Advisory Committee will review the data supporting use of the biomarker and make recommendations to FDA to approve or not approve the submission. FDA would retain the final decision on approval of the biomarker under agreed upon review timeline of [SPECIFIC NUMBER] days.

If FDA rejects the proposed marker or rejects the data package submitted to fulfill a prior agreed BDP, the Agency would state clear rationale and identify any gaps in the Sponsor's submission.

- The program should initially operate as a pilot and, based on experience, could potentially be made permanent and expanded to qualify additional drug development tools (DDTs).
- Opportunities for sharing of best practices and global harmonization of biomarker qualification processes should also be pursued, particularly with Europe.

Overview of Proposals



Expediting the Development of Novel Therapies for Serious or Life-threatening Diseases

FDA's programs for expediting drug development, including Breakthrough Therapy Designation, Accelerated Approval, Fast Track, and Priority Review, "are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks."^{1,2} For patients anxiously awaiting FDA approval of important new medicines, including targeted therapies and treatments for rare conditions, these programs play a vital role in speeding product development while preserving FDA's rigorous standards for safety and efficacy.

Recognizing the importance of these programs for patients, Congress passed the *Food and Drug Administration Safety and Innovation Act of 2012* (FDASIA), which established the Breakthrough Therapy Designation program and expanded the Accelerated Approval program. In the two short years since passage of this landmark legislation, FDA has designated sixty-one Breakthrough Therapies, approved nine Breakthrough-Designated products for ten indications, and has granted seven Accelerated Approvals.

Building upon this record of success, this paper outlines several proposals to further strengthen and expand these programs to approve medicines more efficiently and help spur the development of 21st Century Cures, while ensuring these products continue to meet existing FDA standards for approval of new drugs

- A. Expand Accelerated Approval to Better Leverage Novel Surrogate Endpoints and Post-Market Data Collection
- B. Expedite Development of Breakthrough Designated Products through Modern Clinical Development Strategies
- C. Expedited Access for Breakthrough Therapy Products to Treat Serious AND Life-Threatening Diseases utilizing Real-World Evidence
- D. Support the ADAPT Act to expedite approval based on targeted/limited population studies

¹ FDA, *Guidance for Industry: Expedited Programs for Serious Conditions— Drugs and Biologics*, May 2014, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

² **Fast Track:** Actions to expedite development and review; rolling review.

Breakthrough Therapy Designation: Intensive guidance on efficient drug development; organizational commitment.

Accelerated Approval: Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit.

Priority Review: Shorter clock for review of marketing application (6 months compared with the 10 month standard review)

A. Expand Accelerated Approval to Better Leverage Novel Surrogate Endpoints and Post-Market Data Collection

The FDA Accelerated Approval program has been extremely beneficial to Americans. It permits earlier market availability of therapies for serious and life-threatening illnesses based upon surrogate endpoints or clinical endpoints that can be measured earlier than irreversible morbidity or mortality, while ensuring that these products continue to meet existing FDA standards for approval of new drugs and that clinical benefit is confirmed in the post-marketing period.

Many (nearly 140) new drugs addressing unmet needs in serious illnesses, particularly HIV/AIDS and cancer, have been made available through this program years earlier than would otherwise have occurred.

- Additionally, the potential for Accelerated Approval has provided an important incentive for investment to discover and develop drugs meeting unmet needs in serious diseases.
- In the vast majority of cases, the benefit of the drug receiving Accelerated Approval has been confirmed with post-marketing data.
- In those few cases where benefit has not been confirmed, the system has successfully led to withdrawal of the indication.

There are strong reasons to believe the benefits to the American public would greatly increase with expanded use of Accelerated Approvals.

- Key to the successful use of Accelerated Approval is the ability to collect confirmatory evidence reliably and speedily in the post-market setting. Recent and anticipated adoption of electronic health records (eHR) will greatly increase this ability, facilitating rapid collection of confirmatory evidence from “real world” settings.
- Recent explosive advances in biomarkers (“omics”) and imaging are creating many more candidate surrogates for consideration for Accelerated Approval.
- “The very high success rate of products receiving Accelerated Approval (only 7 of 137 indications withdrawn (5%), with remaining 130 either confirmed or pending confirmation) suggests that the FDA and sponsors have been conservative in applying the standard of “reasonably likely to predict” clinical benefit to identification and use of endpoints for Accelerated Approval.³ In other words, implementation of Accelerated Approval has resulted in the use of endpoints extremely likely to predict clinical benefit, whereas the statute requires that endpoints be reasonably likely to do so. This suggests that a less conservative

³ Analysis of “CDER Drug and Biologic Accelerated and Restricted Distribution Approvals”, Accessed October 2014 and includes data through June 30, 2014, CBER data not available.
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM404466.pdf>

approach would identify additional endpoints which meet the statutory standard thereby providing additional benefit through accelerated availability of important new therapies.

- The preponderance of utilization of Accelerated Approvals for antiviral and oncologic drugs is undoubtedly of multifactorial origin, but anecdotal evidence suggests that several FDA divisions are less open to use of this pathway.
- In addition to finding of an effect on a surrogate endpoint or clinical endpoint that can be measured earlier than irreversible morbidity or mortality, other situations are encountered in drug development in which the general paradigm of Accelerated Approval – approval conditioned upon addressing limited uncertainties in the post marketing period – could be useful.

PROPOSAL:

The FDA should expand the use of Accelerated Approvals of therapies for serious and life threatening illness in the following manner:

1. Facilitate Expanded Use of the Current Pathway by Identifying New Endpoints Meeting Current Criteria for Use for Accelerated Approval.

- For serious diseases and conditions, the agency shall assess, in consultation with external experts where appropriate, potential endpoints for Accelerated Approval.⁴ FDA would not only respond to endpoints that have been proposed by sponsors on a case-by case basis; but the Agency would also proactively and systematically solicit input from patients groups, medical experts, industry, and FDA review teams on which other promising endpoints should be developed to address public health priorities and other areas of unmet medical need. For each such endpoint, the FDA shall determine:
 - Its suitability for use for Accelerated Approval.
 - What additional information might make it usable.
 - What mechanisms of action it might be usable for.
- Each such disease assessment and associated determinations should be signed off on by senior FDA officials to ensure consistency.
- FDA should prioritize these efforts by the extent of unmet need, the extent of drug development activities, and the perceived potential to identify or develop surrogate endpoints.
- FDA shall periodically provide a report to Congress at 2, 4, and 6 years from enactment that discusses the number of products approved utilizing Accelerated Approval, novel surrogate and intermediate clinical endpoints utilized as basis for approval, and approvals by therapeutic area. The report shall also discuss the

⁴ Please see BIO's 21st Century Cures Proposal on "*Biomarker and Surrogate Endpoint Acceptance and Qualification*" for additional details on the sponsor-initiated endpoint review process.

steps FDA has taken to expand and enhance the Accelerated Approval program, the results therefrom, and additional actions the Secretary will take to expand its use more broadly. The report shall also discuss best practices identified by review divisions for utilizing the Accelerated Approval pathway in novel therapeutic areas and how those best practices are being applied across other review divisions.

2. New Basis for Accelerated Approvals:

As noted, the general paradigm of Accelerated Approval could be beneficially applied in additional settings. FDA, in consultation with stakeholders shall develop and implement procedures to allow Accelerated Approvals with post-marketing data requirements and FDA authority to withdraw approval in the following additional settings:

- Where efficacy has been demonstrated in a serious illness or condition and the risk benefit is likely to be favorable but the amount of safety data is less than generally required. Valuable supplemental safety data can then be collected rapidly in real world settings (*e.g.*, from electronic health records and registries).^{5,6}
- Where efficacy (and safety) of a combination of unapproved therapies have been demonstrated in a serious illness or condition, but the FDA determines there are insufficient data establishing that the combination is superior to one or both single agents.
- Where efficacy and safety have been demonstrated in a narrow subpopulation, and FDA has strong concerns that approval might lead to unsafe off label use that could not be controlled by labeling. Post-market assessments would utilize real world evidence to explore the extent and outcomes of off-label use.
- Where efficacy of an antimicrobial agent targeting resistant micro-organisms has been established in one or more indications (*e.g.*, pneumonia), and use for the same organism(s) in a different indication (*e.g.*, sinusitis) is strongly supported by in vitro data, animal studies, PK/PD and/or limited clinical data.⁷

⁵ Importantly, this provision would not change the safety standard; rather, it would facilitate earlier approval of clearly beneficial drugs at a time when the safety profile appears acceptable but the precision and detail of safety information available is less than generally required at approval. In the unlikely case a major safety concern arose later that made the risk unacceptable, the drug could be withdrawn.

⁶ See BIO's 21st Century Cures Proposal on "*Harnessing "Big Data" and Real-World Evidence to Advance the Development of 21st Century Cures*" for additional details on how real-world evidence can be used to advance drug development

B. Expedite Development of Breakthrough Designated Products through Modern Clinical Development Strategies

Purpose: Have Congress provide clear direction to FDA that surrogate and intermediate clinical endpoints can be utilized for the basis of Breakthrough Therapy Designation. FDA's Expedited Programs Guidance states that a "clinically significant endpoint" for Breakthrough Designation includes "an effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)." (p.13) In practice, however, FDA has appeared unwilling to entertain the use of surrogates for Breakthrough Therapy designation, and FDA officials have made public statements that surrogates are not eligible to serve as the basis for Breakthrough Therapy designations.

Further, encourage FDA to accept modern, scientifically rigorous approaches to clinical trial design to expedite the clinical development process and utilize tools such as post-approval commitments to ensure timely access to Breakthrough Therapy medicines when possible.

Proposal: Current Law with Modifications in Blue Underline/Strike-Through:

Eligibility: Sponsor may request a designation as a Breakthrough Therapy and the FDA shall expedite the development and review of such drug if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, ~~such as~~. For the purposes of this paragraph, a clinically significant endpoint may include substantial treatment effects observed early in clinical development, a surrogate or clinical endpoint that meets the requirements of subsection (c)(1)(A), or any other endpoint that the Secretary determines to be clinically meaningful.

- *Actions for Breakthrough Designation Products:* Actions to expedite the development and review of a designated Breakthrough Therapy may include, as appropriate, the following:
 - Holding meetings with the sponsor and review team throughout the development of the drug
 - Providing timely advice to, and communication with, the sponsor to ensure the development program (collection of necessary non-clinical and clinical data) is as efficient as practicable
 - Involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review
 - Assigning of a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor
 - Taking steps to ensure design of the clinical trials is as efficient as practicable when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment
 - Involving senior managers and experienced review staff in discussions with the sponsor the ability to utilize novel endpoints, targeted clinical

[trials, non-traditional clinical trial designs, and additional non-traditional data that support these endpoints and approaches](#)

- [Involving senior managers and experienced review staff to discuss expedited access based on the Sponsor's commitment to conduct post-approval confirmatory studies or complete ongoing long-term efficacy and safety studies](#)
- *Report:* Beginning in 2013, the FDA shall provide an annual report to the House Energy and Commerce and Senate HELP Committees containing information on the number of requests for Breakthrough Therapy designation, the number of products designated by [therapeutic area](#), and a summary of actions taken to expedite the development and review in each case. This report shall be made publicly available.

C. Expedited Access for Breakthrough Therapy Products to Treat Serious AND Life-Threatening Diseases utilizing Real-World Evidence

Purpose: Have Congress provide clear directive for expedited approval and access of Breakthrough Therapy-designated products that treat serious AND life-threatening diseases based on post-approval commitments, such as safety monitoring and the collection of real-world evidence.

Proposal:

- *Eligibility:* Breakthrough Therapy-designated products intended to treat serious **and** life-threatening diseases where no adequate therapies exist and pre-clinical and early clinical testing show the drug is safe and effective for intended population
- *Request for Expedited Approval:* Sponsors meeting eligibility requirements could request expedited approval for drugs where the needs of the intended patient population warrant approval based on early clinical safety and efficacy data (e.g., Phase 2a data)
- *Post-Approval Commitments:* Sponsors would conduct post-approval confirmatory studies that monitor safety and efficacy through the utilization of real-world evidence including, but not limited to:
 - Information collected through a registry or healthcare claims data; or
 - Post-approval trials that confirm clinical benefit; or
 - Completion of long-term safety studies; or
 - Safety monitoring activities such as development of a Risk Evaluation and Mitigation Strategy (REMS)
- *Safety Monitoring by FDA:* FDA would review safety data collected from real-world evidence at pre-determined intervals to ensure a continuing positive risk-benefit profile
- *Procedures for Withdrawal:* The FDA may withdrawal approval if:
 - Sponsor fails to conduct required post-approval studies

- Other evidence demonstrates that the product is not safe or effective under the conditions of use
- *Report:* FDA would provide a report to Congress 2 years after enactment discussing how real-world evidence collected under this program will be utilized to inform the development of standards and methodologies for the utilization of real-world evidence in drug development and review processes more broadly.

D. Expedited Approval based on Targeted/Limited Population studies

Support the *Antibiotic Development to Advance Patient Treatment Act (ADAPT Act, H.R. 3742)*, sponsored by Congressman Phil Gingrey (R-NY).

Modifications in *Blue/Underline*

- *Eligibility:* At the request of the sponsor of an antibacterial or antifungal drug intended to treat a serious or life-threatening disease or condition, the Secretary may approve a drug to treat a limited population of patients for which there is an unmet medical need.
- *Evidence:* In determining to grant such approval for a limited population of patients, the FDA may rely on traditional endpoints, alternative endpoints, or a combination of traditional and alternative endpoints; datasets of limited size; pharmacologic or pathophysiologic data; data from phase 2 clinical studies; and such other confirmatory evidence as the Secretary deems necessary.
- *Labeling:* The FDA shall require the labeling of drugs approved pursuant to this subsection to prominently include in the prescribing information required by section 201.57 of title 21 of the Code of Federal Regulations (or any successor regulation) the following statement: This drug is indicated for use in a limited and specific population of patients. Such labeling may be removed if drug is subsequently approved or licensed under section 351 of the Public Health Service Act.
- *Relation to other provisions:* Nothing in this subsection shall be construed to prohibit designation and expedited review of a drug as a Breakthrough Therapy under section 506(a), designation and treatment of a drug as a Fast Track product under section 506(b), or Accelerated Approval of the drug under section 506(c), in combination with approval of the drug for use in a limited population of patients under this subsection.
- *Rule of construction:* Nothing in this subsection shall be construed to alter the standards of evidence under subsection (c) or (d) (including the substantial evidence standard in subsection (d)). Subsections (c) and (d) and such standards of evidence apply to the review and approval of drugs under this subsection, including whether a drug is safe and effective. Nothing in this subsection shall be construed to limit the authority of the Secretary to approve

products pursuant to this Act and the Public Health Service Act as authorized prior to the date of enactment of this subsection.

- ADVICE.—The Secretary shall provide prompt advice to the sponsor of a drug for which the sponsor seeks approval through the limited population pathway for antibacterial drugs to enable the sponsor to plan a development program to obtain the necessary data for approval of such drug through the limited population pathway for antibacterial drugs and to conduct any additional studies that would be required to gain approval of such drug for use in a broader population.
- GUIDANCE.—Not later than [12 months] after the date of enactment of the Act, the Secretary shall issue draft guidance describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial drugs. The Secretary may approve antibacterial drugs through such limited population pathway prior to issuing guidance under this paragraph.
- EVALUATION: Within [18 months] of enactment, the Secretary shall publish for public comment an assessment of the program conducted by an independent contractor. The statement of work for this effort will be published for public comment prior to beginning the assessment. The assessments will occur continuously throughout the course of the program. This assessment will include interviews of the sponsor and FDA, as appropriate. The assessment shall determine if the limited-use pathway has or is likely to improve patient access to novel antibacterial treatments and assess how the pathway could be expanded to cover products for serious or life-threatening diseases or conditions beyond antibacterial infections. FDA will hold a public meeting within 90 days of publication to discuss the findings of the assessment, during which public stakeholders may present their views on the success of the program, and the appropriateness of expansion to serious or life-threatening diseases or conditions.
- EXPANSION OF PATHWAY.—If the independent assessment determines, based on the experiences demonstrating increased number of new indications for antibacterials and antifungals, that other therapeutic areas would benefit from expansion of the limited population pathway for antibacterial drugs, the Secretary may expand such limited population pathway in accordance with such a determination. The approval of any drugs under any such expansion shall be subject to the considerations and requirements described in this subsection.

Harnessing “Big Data” and Real-World Evidence to Advance the Development of 21st Century Cures

I. SUMMARY

As Electronic Health Records (EHRs) and e-prescribing systems are integrated into the U.S. healthcare delivery system, a vast amount of information on the utilization of healthcare interventions and associated medical outcomes will be collected and stored. The confluence of health information technology, “big data” analytics, and modern biomedical research represents a remarkable opportunity to develop new methods for utilizing Real World Evidence (RWE) to assess the benefits and risks of drugs and biologics in a manner that is more efficient and expeditious than randomized controlled clinical trials (RCTs). However, additional progress must be made to develop and validate methodologies for evaluating real-world data to inform regulatory decision-making, particularly for assessing effectiveness.

This paper proposes:

- Facilitating researcher access to government data sources under responsible patient privacy, security, and confidentiality safeguards.
- A private-public partnership to develop, validate, and pilot methodologies for interrogating EHRs and real-world data to assess medical outcomes and support claims of safety and effectiveness.
- An approval mechanism for therapies intended to treat serious diseases and conditions, based on clinical evidence that indicates a drug may demonstrate substantial improvement over existing therapy and has a positive benefit-risk profile for its intended use, followed by monitoring of safety and effectiveness through the collection of real-world data. Confirmation of the benefit-risk profile or any expansion of the approved indication in the post-market setting may still require RCTs, but the process should incorporate evidence from RWE, including observational data and pragmatic designs. This should reduce any burden of RCTs and result in more quickly identifying and reaching the patients that would most benefit from the drug.

II. BACKGROUND

The United States’ national investment in the wide-scale adoption of electronic health records places biomedical sciences at the cusp of fully realizing a “learning healthcare system.” *The American Recovery and Reinvestment Act of 2009* authorized the Centers for Medicare & Medicaid Services (CMS) to provide incentive payments to eligible professionals and hospitals who adopt, implement, upgrade, or demonstrate meaningful use of certified EHR technology through three successive stages between 2011 and 2016. Smart phones and wearable technology, including fit-bands and smart watches with

biometric sensors, also hold great promise to unlock real-time information on personal health and wellness that can be directly integrated into EHRs with the patient's consent. In light of this ongoing revolution of health information technologies, policymakers should evaluate how real-world data can be utilized to assess the safety and effectiveness of medical interventions, including drugs and biologics, to support the cycle of biomedical innovation from drug discovery and development to the point of healthcare decision-making.

Continued technological advances in gathering and employing data have the potential to improve the timeliness of drug development without impacting high standards for quality and safety.ⁱ For example, while randomized, controlled clinical trials are considered to be the gold standard to assess safety and clinical efficacy, they often evaluate uniform populations remotely connected to the use of drugs in regular clinical practice or in settings reflecting real-world health care delivery. RCTs can readily identify higher-frequency adverse events and assess clinical efficacy, but they must enroll thousands of patients to be powered sufficiently to detect rare adverse events or slowly progressing clinical manifestations. However, increasing the size, length, and complexity of clinical trials is not an economically sustainable option and places further burdens on the ability of researchers to enroll and conduct clinical trials feasibly.

FDA, sponsors, and academics should be actively working to integrate real-world data into the drug development and review process in a scientifically robust manner to achieve the right balance of what evidence is required before and after approval. We should pursue approaches that more closely integrate reasonably sized pre-market clinical studies and real-world data with mandatory post-market surveillance and analysis of additional real-world data to assess safety and effectiveness further and to refine the therapy's benefit/risk profile.ⁱⁱ

Unlocking real-world evidence for analysis can also be used to complement the existing clinical trial process, for example as by guiding hypothesis generation to improve the likelihood of trial success or helping to identify and enroll patients in studies. EHRs embedded in clinical care could also help to establish large-scale patient registries, facilitate "virtual" control arms for interventional trials, or learn about medical interventions in a post-market setting, such as by replacing post-market Phase IV studies in some circumstances.

Real world data and analytical methods must be accessible in a manner that is standardized, interoperable, and validated for regulatory purposes. As part of the Agency's Sentinel Network initiative, FDA has made considerable progress in developing the tools and methodologies for assessing post-market data to identify safety signals; we should continue to build upon that foundation to also consider efficacy endpoints. The scientific methods in this area continue to evolve—and are evolving in particular through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program.ⁱⁱⁱ Additionally, the Patient-Centered Outcomes Research Institute (PCORI) has invested more than \$100 million in the development of PCORnet, a "national network for conducting clinical outcomes research. PCORnet will foster a range of observational and experimental CER by establishing a resource of clinical data gathered in "real-time" and in "real-world" settings, such as clinics."^{iv}

We must embrace a future where FDA, academia, and industry can be aligned to better leverage real-world data to answer key research questions more efficiently than in large RCTs.

III. PROBLEM STATEMENT

Despite the rapid growth in healthcare information technology and the implementation of EHRs, data is often non-standardized and stored in government databases that are inaccessible to researchers. Additionally, there is no clear process for developing and validating methodologies for interrogating real-world evidence, and qualifying these approaches for use in FDA regulatory decisions. Furthermore, FDA's clinical development paradigm should be updated to accommodate the use of real-world data for demonstrating safety and effectiveness.

IV. PROPOSAL

1. *Unlocking Data Sources for Research Purposes:*

Enabling the appropriate use of rapidly growing digital health information can help not only to inform regulatory approval and in fulfilling post-approval commitments, but also in providing relevant information at the point of healthcare decision-making. Crucial to this effort will be broadening access to existing federal data resources—such as from Centers for Medicare and Medicaid Services (CMS)-administered federal healthcare programs, NIH, and the Centers for Disease Control and Prevention—and standardizing the collection of these data across various sites of care to provide a comprehensive, continuous picture of an individual's health and the care he/she receives. Congress should authorize qualified researchers and research collaborations (including partnerships with the biopharmaceutical industry) to access certain data sources under appropriate patient privacy, confidentiality, and security safeguards. This will help researchers to better understand the natural history of diseases and to facilitate the evaluation of new medical interventions.

Specifically, such data sources may include:

- Electronic Health Record Data (*de-identified or aggregated*)
- Medicare Claims Data, including Part D, and Exchange Data
- Pooled Clinical Data from Federally Funded Clinical Studies
- Veterans Administration and National Institutes of Health Medical Data
- FDA Mini-Sentinel
- PCORNet

Specific activities to unlock the data for research purposes would include:

- Standardizing the collection of data across federal data systems;
- Broadening access to federal data resources; and
- Investigations to understand natural history of diseases and facilitate the evaluation of new medical interventions. The evaluation of new medical interventions is not based on the methodology to be developed by the PPP below, but rather it uses the additional information about natural history to facilitate development programs.

This process should also recognize that data systems will change and evolve in the rapidly advancing technology marketplace. As data and delivery systems become more sophisticated over time they will become more powerful tools for collecting data, storing

and analyzing data, and making research findings available to researchers and policymakers. Consequently, flexible approaches are necessary to accommodate technological advancement as system capacities expand.

2. Analytics and Methodology Development:

Congress should also authorize a private public partnership to develop, validate, and pilot methodologies for using EHR and real-world data for regulatory purposes, including FDA approval. Such a partnership would assess key challenges and current limitations related to the use of real-world evidence to advance medical product development and identify potential solutions.

The private-public partnership would include the NIH, FDA, the National Coordinator for Health Information Technology, the biopharmaceutical industry, academia, professional societies, patient groups, and EHR standards setting bodies and vendors. Participating organizations would provide technical experts including biostatisticians, clinicians, epidemiologists, bioinformaticians, software engineers, privacy experts, and other thought leaders. The partnership would be established under the auspices of a credible umbrella organization, such as the Reagan-Udall Foundation for the FDA, and would be funded through a mix of Federal funding and private donations and grants. Successful private-public partnerships such as the European Innovative Medicines Initiative (IMI) could be used as a model to identify both best practices and lessons learned.

The PPP would examine the interoperability and standardization of relevant EHR data fields and identify solutions to trace an individual product to a medical outcome. Furthermore, the PPP would promote methods for improving data quality and establishing standards of how to extract data from various sources and EHRs.

The partnership would also lead the development of a common platform overlaying existing databases that would allow researchers to access and query real-world data in a structured, centralized fashion using commonly accepted and validated query methods, protocols, and algorithms.

The PPP would also be authorized to issue competitive grants to pilots and conduct proof-of-concept studies to support regulatory qualification of the methodology.

Recommendations from the PPP on study methodologies and how real-world evidence can be used to support safety and efficacy claims would be evaluated by FDA and issued as formal guidance for public comment. FDA could also join in pilot programs where few select companies collaborating closely with the FDA evaluate, in small indications, different uses of RWE in support of safety and/or efficacy claims.

Specific analytics and methodologies developed by the partnership would address:

- Electronic Health Record Data:
 - Improving EHR data quality
 - Standardizing EHR systems and make them interoperable across different EHR formats and data systems
- Patient Privacy, Security and Confidentiality

- Protecting patient privacy and security, both with respect to technical approaches (encryption, firewalls) and policy (legislation, regulation)
- Protecting commercially confidential information
- Drug Development Applications:
 - Developing and validating methodology for use of RWE, particularly for effectiveness assessments
 - Recommendations on how RWE can be integrated into drug development to support FDA regulatory decision making. For example:
 - Facilitating the identification and enrollment of qualified patients in clinical trials
 - Establishing large-scale patient registries using EHRs
 - Serving as “virtual” control arms in interventional trials
 - Replacing traditional Phase IV studies with studies enabled by EHRs
 - Demonstrating effectiveness in a post-market setting

3. *Real-World Evidence Development Pathway:*

Congress should also update FDA’s approval pathways to better utilize real-world evidence. Traditionally, FDA approval is based upon two adequate and well-controlled clinical investigations or “data from one adequate and well-controlled clinical investigation and confirmatory evidence.” While FDA has often interpreted these provisions to require randomized, controlled clinical trials in most instances, “confirmatory evidence” can also be based upon real-world evidence collected in either a pre-market or post-market setting.

This new approval mechanism would be for therapies intended to treat serious diseases and conditions, based on clinical evidence that indicates a drug may demonstrate substantial improvement over existing therapy, followed by monitoring of safety and effectiveness through the collection of real-world data. For example, confirmation of the clinical benefit for drugs approved under Accelerated Approval could be based upon an analysis of RWE. Additionally, expansion of the approved indication in the post-market setting may still require RCTs, but the process should incorporate evidence from RWE, including observational data and pragmatic designs. This may reduce the burden of RCTs and result in more quickly identifying and reaching the patients that would most benefit.

REFERENCES:

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ⁱⁱ Kocher and Roberts, *the Calculus of Cures*, *New England Journal of Medicine*, April 17, 2014, <http://www.nejm.org/doi/pdf/10.1056/NEJMp1400868>

ⁱⁱⁱ Reagan-Udall Foundation for the FDA, *IMEDS Program Overview*, <http://www.reaganudall.org/our-work/safety-and-better-evidence/imes-program/>

^{iv}PCORI, *PCORnet: The National Patient-Centered Clinical Research Network*, <http://www.pcori.org/funding-opportunities/pcor-net-national-patient-centered-clinical-research-network/>



Improving Patient Access to Experimental Therapies Through Effective Expanded Access Processes

I. SUMMARY

Expanded access is an important issue for patients who may face life-threatening conditions that have no appropriate therapy and for whom an unapproved drug may be the only possible treatment option. This issue has come to the fore principally as the result of highly publicized cases where access to an unapproved drug was not possible. This has raised the question of what policy or process changes might improve the current situation for patients.

Several approaches are suggested here for improving how companies and FDA deal with individual-patient requests for unapproved drugs and potentially improving outcomes for patients. These proposals attempt to improve coordination and communication between FDA and companies before final decisions are conveyed to the patient/physician and address the perception and possibility that providing access to an unapproved drug may have an adverse effect on the ability to complete development and provide access to approved product for all patients who need it.

II. BACKGROUND

Companies try to meet patient needs for unapproved drugs in several ways. Established expanded access programs, approved by FDA, may provide access for a limited number (the number depending on the situation) of patients who do not qualify for, or are unable to participate in ongoing or planned clinical trials of a drug candidate. Additionally, companies may be able to provide access for individual patients through a "compassionate use" or related emergency access process, used in a situation where the unapproved drug may be the only viable option for a patient in an urgent or intractable medical situation. A number of companies have well-established public policies regarding how they will respond to requests for such individual-patient access to their experimental drugs. Such companies generally try to adhere to those policies relatively firmly, regardless of public and media pressure. In other cases, urgent individual requests for an unapproved product pose difficult challenges that may be exacerbated by inadequate communication among a company, FDA, and requestors, particularly if it does not take full account of valid limitations on the ability of the company to supply the drug. This may result in difficulties for the company and, most importantly, confusion, disappointment, and distress for patients and their treating physicians, caregivers, and families.

The growing use of social media, which allows the near-instantaneous participation of thousands of individuals, can complicate matters further. Patients and families in desperate situations understandably can be expected to turn to Facebook, Twitter, Instagram, and other mechanisms to get their stories to tens of thousands of people who then bring increased pressure. This publicity, along with personal appeals from constituents, has prompted interest among both federal and State legislators in addressing and improving patient access to experimental medicines. Several States already have passed laws that would make experimental medicines available to patients without FDA's approval and would

protect physicians and others from adverse legal action for recommending or supplying such unapproved medicines to patients. In general, while these State bills purport to guarantee access, they create false hope that patients automatically will be able to access unapproved drugs. Such laws tacitly suggest that every company is capable of supplying the desired drug and may do so without FDA authorization. The latter is never true, and the former may, unfortunately, not be the case either, for a variety of reasons. Such false hope and misguided assumptions do not effectively address the pressing needs of patients.

Some in Congress also have added their voices to the debate and intend to take legislative action at the national level that could address current concerns in a way that is acutely sensitive to the needs of patients but also recognizes limitations on companies' abilities to respond affirmatively in every situation.

There are a number of valid reasons that companies are hesitant or unable to provide drugs outside of their clinical development programs.

- At the time of the request, the patient may be eligible to participate in an existing expanded access program or an open-label clinical trial, or may benefit from an available and appropriate approved treatment of which the physician and patient may be unaware.
- The not-yet-demonstrated safety of the product, as well as unproven efficacy, makes the assessment of benefit-risk virtually impossible. Early-phase, seemingly positive results can be difficult to understand and may suggest that a medicine will be beneficial when in reality there may be little or no activity against a particular condition. This has particular relevance if the use of the drug candidate is being sought for a patient whose condition is not the one for which the drug is being tested—even the most promising results from clinical studies may be completely inapplicable to patients with other conditions or in medical situations much different from those of patients enrolled in the clinical trials. In those cases, the expanded-access patient may be placed at risk greater than that of the condition for which the drug is sought, with virtually no possibility of benefit. The risk in this situation could arise from the possible side effects of the drug or from the time lost receiving a potentially ineffective drug when other avenues of treatment might have been pursued. Companies do not want to place patients at risk without an expectation that the benefit will outweigh that risk.
- Production capacity may constrain the amount of drug a company can supply prior to approval, which may mean that, even if the company is willing to offer expanded access, supply may be quite limited and not available to all patients. This raises the question of fairness—how does a company choose one patient over another? Will the patient who asks for the drug in January get it, and the patient who asks in June be denied? This not only may create an ethical dilemma, but also may sap resources that are better used to complete development so the drug can be approved and all patients can have equitable opportunity to access a safe and effective drug.

Additionally, it is often difficult to produce sufficient product for patients in clinical trials, a difficulty that could be exacerbated by the need to produce product for an unknown number of patients outside of those trials. This may be the case for several reasons, including that the manufacturing process generally is not yet finalized for commercial production. Having to supply an unanticipated number of doses, often in an unpredictable timeframe, potentially jeopardizes availability even for patients

enrolled in trials – a situation that could cause a slowing of the development program and approval of the product.

- Allowing access to unapproved medicines outside of clinical trials can place trial enrollment at risk and slow development, thus protracting the regulatory approval that makes safe and effective medicines available for all patients who need them.
- Finally, it is difficult to know with certainty how FDA will evaluate information from cases where patients have used an experimental medicine. For example, clinical outcomes such as adverse events are seen that may not appear to accord with data from controlled and monitored clinical trials. More clarity on how FDA will treat such information is needed to ensure expeditious patient access to potential life-saving treatments. If regulatory concerns about that information lead to a slowing of the development program, through requirements for additional studies for example, all patients waiting for the therapy will suffer.

III. PROBLEM STATEMENT

There is strong Congressional interest in addressing the Expanded Access issue in the context of the 21st Century Cures initiative—particularly for single-patient, emergency use situations. There is an opportunity, in that context, to suggest approaches that may satisfy legislators’ desire to address the issue.

Addressing current concerns can begin with finding ways that FDA and companies can communicate more effectively and efficiently when expanded access is requested, so decisions are made not only in the best interest of patients but also with a full understanding of the company’s limitations with regard to supplying product and its need to advance its development program. While there are processes in place for FDA to authorize expanded access use, these processes, as defined in regulation, do not directly consider the company’s ability to provide the drug under a treatment, emergency, or single-patient IND. Routinely established expanded access programs, particularly for therapeutics being developed to meet significant unmet medical needs (e.g., Breakthrough-designated or Fast Track products), may help patients. Since such therapies can be expected to be in high demand pre-approval, this approach might help patients in need, lower the number of urgent requests, and allow development programs to move forward expeditiously.

IV. PROPOSALS

The following are proposed (these proposals are neither mutually inclusive or exclusive nor interdependent):

- **Require enhancements in FDA education and communication.** This should include improvements in information for patients and providers seeking expanded access (including information on FDA’s website), to improve education and facilitate information gathering; simplification of agency procedures and requirements for seeking single-patient/emergency access, including IRB approval and patient informed consent; training for healthcare providers and other stakeholders; and additional training for FDA staff on the issue and the process. Through these materials and communications, it should be made clear that the decision to establish an expanded access program is multi-factorial and often complicated.

- Require that FDA consult with the sponsor (such consultation may be presumed if the sponsor has submitted an IND application or indicated to FDA its intention to do so) as soon as possible after FDA receives a request for emergency access to an unapproved drug to ensure that consistent messages are conveyed to treating physicians and patients. Consistent responses to requestors help to prevent confusion and disappointment, which exacerbate an already difficult situation. All communications should make clear that the decision process considers multiple critical issues.
- **Encourage and help facilitate the establishment of expanded access programs** early in drug development, for drugs designated Breakthrough Therapies [or Fast Track products or that are determined by FDA to be expected to meet a significant unmet medical need], for companies that are small businesses and for which establishing such programs is a significant challenge. Such expanded access programs would be available to patients under conditions established by FDA and the sponsor, which may include limitations on total number of patients (although equitable access would be an essential component), disease indications, timeframe, or other criteria. The existence, availability, and any limitations of these expanded access programs would be made public, including by listing on ClinicalTrials.gov as well as by other mechanisms. Such expanded access programs would be established and available in such a way as not to jeopardize the enrollment or execution of clinical trials.
 - If FDA determines that expanded access is likely to be beneficial to patients (*e.g.*, high unmet need, lack of alternative therapies, serious disease, very promising early data, etc.), FDA will work with a sponsor that establishes such a program to help identify the most efficient and effective path to approval (provided the drug is demonstrated to be safe and effective). This FDA–sponsor interaction will also include discussion of whether and how data collected in the expanded access program might be used to accelerate the path to approval.
 - Explore potential financing mechanisms for small businesses to implement expanded access programs.
- **Establish a clear and structured approach for FDA consideration of data and information from expanded-access use.** Require that FDA make clear, in writing, the way the agency will treat any expanded-access information (particularly in the single-patient emergency access situation), to make clear that such evaluation will be fully consistent with existing regulation and guidance, across FDA divisions and offices. Require that FDA consider specifically that data and information derived from expanded-access use of the drug (particularly in an emergency-access, single-patient situation) generally come from a setting that is not as well controlled and well monitored as registration trials, and patients who receive drugs outside of clinical trials might not have qualified for the trials because of factors that, for example, could affect the number, type, or degree of adverse events. For example, the disease in such patients may be significantly advanced, the patient may have numerous concomitant health problems or may be using multiple other therapies, the patient’s age may be significantly outside the age parameters of the clinical trials, etc. (Similarly, when FDA receives adverse event reports regarding approved drugs, the agency evaluates them in context and considers action only after taking into account the situation in which the event occurred and working with the sponsor

to evaluate such information.) Such a legislative requirement would be consistent with FDA existing regulation and would give that approach the force of law.

In a case where FDA determines that further study is necessary to evaluate the validity or impact of the data or information from the expanded-access use, the sponsor may be required to conduct such study post-market. However, the ongoing development program may not be delayed or stopped as a result of receiving such data or information or requiring further study (i.e., generally, such additional study would not be required pre-approval to prevent an adverse impact on development time).

In a case where serious adverse events are reported that also have been seen in patients enrolled in the clinical trials (or can be anticipated to occur based on the nature of patients being enrolled or the trial design), FDA may require additional data before approving the product. Prior to making such a determination, and as soon as the information has been evaluated, FDA and the sponsor will meet for the purpose of reaching agreement about the nature and timing of any studies or data that would be required before FDA's action on the sponsor's application. FDA and the sponsor will determine a mutually agreeable date for the meeting, and the sponsor will have an opportunity to provide its own assessment of the information.

The agreement regarding studies or data will be confirmed in writing by FDA, with the sponsor having an opportunity to review and provide comments to the document before it becomes a part of the FDA administrative record. The agreement will be binding on both parties. FDA will not change the requirements without the written consent of the sponsor or if the director of the applicable review division determines that a new or unanticipated scientific issue that relates to the safety of the drug requires such a change. In such a case, FDA will notify the sponsor in writing and provide a prompt meeting opportunity to discuss the matter.



Longitudinal Study to Identify Genetic and Other Predictors, Precursors, & Signs of Alzheimer's and Other Diseases¹

I. SUMMARY

This proposal is for the development and execution of a large-scale, longitudinal study that will include sequencing the genomes of individuals in age cohorts through age 90 and obtaining samples from those individuals of biological markers that may predict Alzheimer's Disease (AD) or other chronic diseases for which the cause is unknown or poorly understood.

II. BACKGROUND

The impact of chronic disease on a number of economic indicators, including employment, workplace productivity, and overall healthcare costs, is enormous. Effectively managing chronic diseases and mitigating their economic impact pose significant challenges for the healthcare system, even in instances where the disease cause is well-understood and can be predicted in advance of symptoms. When the cause is unknown, and the disease has progressed significantly before it is detected, the challenge is astronomical. In light of current demographics, the extraordinary reach of chronic disease will overwhelm the U.S. healthcare system in a relatively short time. While AD is only one such chronic disease, it represents one of the best illustrations of the problem and is expected to have the largest system-wide impact.

An estimated 24 million people worldwide have dementia, most from Alzheimer's disease. That number is predicted to double by 2020 – just over 5 years from now – and triple by 2040. The numbers are equally striking for the U.S., where over 5 million people over the age of 65 are afflicted today – a number that is expected to triple by 2050. The financial cost to the healthcare system of caring for individuals with AD is estimated at over \$200 m today and will rise to over \$1 trillion by 2050. The societal costs are inestimable. These predictions do not include individuals with early-onset AD, who are under the age of 65 at first onset or diagnosis. Without an intervention that prevents the disease, delays or slows its progression, or cures it, AD alone will overwhelm the U.S. healthcare system within the next 25-30 years. This is simply an untenable situation.

It is well recognized that a first step toward addressing this enormous problem is to try to identify the cause of the disease, individuals who are at risk for the disease, and potential targets for intervention. Public and private entities worldwide are engaged in

¹ This proposal is inspired and informed by, and attempts to build on, ideas and work by key stakeholders such as Dr. Moncef Slaoui, Chairman of Global Research and Development, GlaxoSmithKline; Dr. Leroy Hood, President, Institute for Systems Biology, Seattle; Banner Health and the Banner Alzheimer's Institute, Phoenix; George Vradenburg, Chairman and Founding board member, UsAgainstAlzheimer's; Dr. Francis Collins, Director, NIH; Dr. Richard Hodes and others at the National Institute on Aging (NIA); various NIA grantees; and others.

efforts to understand AD, to determine how best to develop therapies, and to address the enormous challenges facing caregivers.

In the U.S., many such efforts also are under way, in part as a result of the mandate of the *National Alzheimer's Project Act*² (signed into law in January 2011) and under the National Alzheimer's Strategic Plan. There is recognition that the multiple efforts relating to AD need to be coordinated effectively for the greatest possibility of a return on investment and to expedite obtaining information essential to prevent the predicted a disastrous outcome. It is not for lack of desire to address the current and impending impacts of chronic disease in general and AD in specific. Indeed, from the perspective of the biopharmaceutical industry, this is a top priority. However, the high failure rate of potential AD treatments in particular discourages R&D and investment.

There is broad agreement that biologic and drug development moving forward can be accelerated through public-private partnerships that bring together knowledge, skills, and expertise, as well as funding, from the public and private sectors to enhance what each sector is capable of doing on its own. Such partnerships and consortia already are making progress in a number of areas with high public health impact, including AD. For example, the international Genomics of Alzheimer's Project (IGAP), which combines the efforts of the Alzheimer's Disease Genetics Consortium, the Cohorts for Heart and Aging Research in Genomic Epidemiology, the European Alzheimer Disease Initiative, and the Genetic and Environmental Research in Alzheimer Disease consortium, have worked together to identify Alzheimer's genetic risk factors – identifying more genes through this cooperative effort than had been identified in the previous 20 years. While this work is groundbreaking, more importantly it opens doors for further study that can incorporate technology such as genome sequencing to elucidate further the risks, causes, and targets for intervention in AD.

The complexity of AD extends as well to phenotypic heterogeneity. For example, patients may be affected by the disease for years without obvious cognitive impairment, while in others such impairment is obvious at the earliest stages of the disease. This type of complexity hinders researchers' ability to identify genetic associations and variations and reinforces the need for very large study cohorts that include a broad range of phenotypes.

A study of the magnitude and scope necessary to provide the greatest chance of success is beyond the capacity of a single institution or company, and would require a large number of investigators and study sites, funded over an extended period of time. New government funding would be essential for this, as taking funds from existing research would slow or prevent progress in other significant areas. While the study could focus on AD, it also could extend well beyond that disease to other chronic conditions, about which information would be obtained through the genomic sequencing and other biomarkers associated with the study participants. Observing and taking biological samples from these participants over a period of time from 10 to 30 years would yield a huge cache of information that could help identify targets for preventing and treating not only AD, but also other chronic diseases.

² *National Alzheimer's Project Act*, Pub. L. No. 111-375 (2011)

III. PROPOSAL

This multi-step, multi-year program will begin with the convening of experts in the areas of, for example, chronic disease, AD, genetics and genome sequencing, design and execution of longitudinal studies, as well as patient organizations. Prior to such a meeting, there should be discussions with a smaller number of key individuals regarding who the participants in a larger meeting should be and how to facilitate the discussions. This initial meeting would lay out general concepts, identify key questions and topics, and organize the group into sub-groups on the identified issues. Importantly, the meeting would discuss how this project will add to what is already being done, particularly in the area of Alzheimer's Disease, and how this project can effectively be integrated with a number of other projects, including the Alzheimer's Disease Sequencing Project and other activities under way as part of the National Plan to Address Alzheimer's Disease. Among the questions to be answered is what resources would be anticipated to initiate the study and to carry it out over decades. Clearly, the scope and length of the study is one critical factor in estimating cost.

The study will require substantial federal funding, presumably from the National Institutes of Health (NIH), but should not secure that funding by reducing other important NIH research or requiring re-alignment of NIH research priorities. This should be entirely new funding.

Optimally, this activity will be funded and administered through a public-private partnership, with private partners also contributing funding and making in-kind contributions (e.g., personnel). The development of such a partnership will require outreach to the private sector, along with traditional fundraising. The nature of the public-private partnership, including such questions as sharing data, use of results, development of products, intellectual property, etc., will merit discussion.

A subset of the experts designing the study could serve as a scientific advisory board; additional experts can serve as the project's coordinating committee. Accountability for federal funds would be via annual reports to the funding agency or institute (NIH/National Institute on Aging) and to relevant Congressional committees. A principal investigator would be responsible for ensuring these reports are timely and accurately submitted, and include input from all investigators in the project.

The project would be designed so that health research, drug developers and other entities engaged in similar studies and analyses could both input their data into this study and download data from it.

In general, the parameters of the study and enrollees would be:

- Multi-investigator;
- Networked clinical sites;
- Geographically distributed;
- Enrollment of age cohorts 40-50, 50-60, 60-70, and 70-80 (cohorts and total number of enrollees to be discussed with experts at meeting);
- Significant education effort to encourage enrollment (including electronic means including social media), possibly combined with assistance from existing longitudinal studies (e.g., Framingham Heart Study, Nurses' Health Study, Baltimore Longitudinal Study of Aging), whose participants may be willing to enroll as well in this study;

- Ethnic and gender diversity and appropriate representation;
- Study participants followed and monitored (including collection of biological samples) until age 90 or death;
- Common protocol and networked sites, to ensure consistent data collection methodology, elements, and formats;
- Use of modern tools for enrollment and monitoring of participants, including enrollment via electronic means, long-distance collection of biological samples (samples and test results collected in central repositories), electronic communication between investigators and enrollees and among investigators, etc.;
- A central IRB (initial protocol and modifications);
- A central data repository with analytical capability with the data available for use by researchers, product developers, and others (whether part of the study or not), and the repository also could accept data from researchers, drug developers, and others engaged in similar or related studies;
- Development of data queries, with input from all sites, and regular queries (annual? biannual?) for pre-specified information; and
- An established publication policy.

The overall goal of the study is a deep understanding of AD (and other chronic diseases) that will facilitate the identification of biomarkers for diagnostic tests and therapeutics and development of targeted biopharmaceutical approaches to prevention and treatment, including products that will delay the onset of disease or of disabling symptoms. The “moon shot” is a cure.

The project would be managed either by NIH (through NIA), a private organization, or a mechanism established by the advisory board and coordinating committee.

Incentives for Research and Development of Antibiotics, Novel Treatments, Vaccines, and Biological Approaches to Combat Antimicrobial Resistance

I. SUMMARY

Antibiotics and vaccines are essential cornerstones in modern medicine and key components in protecting the public health. However, the continuing growth and evolution of antibiotic resistance threatens modern medicine and public health.

While we have been encouraged by recent activities on this issue by the Administration and Congress, more work is needed. Continued research into new antibiotics, coupled with strategies for novel antimicrobial biologics such as modern antibodies and vaccines could have significant high value impact on unmet medical needs. It is imperative that research and development (R&D) efforts in this are vigorously supported. As Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA), noted at a recent 21st Century Cures public hearing on antimicrobial resistance, the U.S. currently does not have a robust pipeline of antibiotics and we need treatments urgently both for existing and emerging threats. The public health threat caused by antibiotic resistant infections is made more dire by the fact that biopharmaceutical companies face formidable economic and regulatory challenges in discovery, development and delivery of infectious disease products.

This paper discusses challenges surrounding antimicrobial drug and vaccine development, specifically against an increasing array of antibiotic-resistant pathogens and lays out a proposal for greater incentives for development of products that address the 18 pathogens on the Centers for Disease Control and Prevention (CDC) threat list.

II. BACKGROUND

Antibiotics and vaccines have long been considered two of the most important medical interventions of the last century, enabling and underlying the practice of modern medicine as we know it. Preventive vaccines have significantly reduced and even eradicated many diseases that used to be among the most common and lethal childhood infections. The development of antibiotics permitted revolutionary surgical procedures (*e.g.*, transplants) and allowed life-saving therapies following such procedures (*e.g.*, immunosuppressive therapies). While public health has greatly benefitted, the overuse of broad-spectrum antibiotics eventually led to the rise of antibiotic-resistant bacteria that now represents a significant threat to public health.

Many of these pathogens could be reduced or perhaps even eliminated with the application of a broader infectious disease strategy that strongly incentivizes the



continued development of antibiotics and also incentivizes biological drugs such as antibodies, vaccines and other new infectious disease products to prevent and treat infections in high risk patients.

Over the years, the pipeline of new antimicrobial drugs has consistently decreased while the number of patients suffering or dying from infections resistant to current treatments is rising. Some initial progress has been made in spurring R&D in new antibiotics over the last two years, primarily due to the incentives and other provisions in the Generating Antibiotics Incentives Now (GAIN) Act. With the implementation of the GAIN Act, the FDA has designated several new antibiotic candidates as qualified infectious disease products (QIDP) and has approved a few of such products.

While this initial progress has been helpful, there are still several regulatory and reimbursement barriers that must be addressed to prevent, diagnose and treat serious bacterial infections if we are to affect the necessary paradigm shift to meet the ongoing challenge of antibiotic resistance.

Successful efforts to reduce the morbidity, mortality and economic impact of antibiotic-resistant bacteria and other drug-resistant pathogens will require a coordinated multi-pronged strategy and a sustained effort that leverages modern powerful technologies in addition to new mechanism antibiotics, including vaccines, novel focused-spectrum monoclonal antibodies, innovative treatments, devices and prevention options coupled with point-of-care diagnostics.

III. PROBLEM STATEMENT

Given the diversity of bacterial infections and susceptible patient populations, a broader discovery approach that includes new treatment and preventive modalities are needed. A broader research agenda should encourage investment and partnership between industry, academia and government to bring new antimicrobials, biologics, vaccines and diagnostics to market. A comprehensive multi-pronged national strategy investing across the continuum of drugs, biologics, vaccines and diagnostics targeting resistant pathogens could lead to:

- A decrease in the incidence and emergence of resistant pathogens.
- The preservation, and perhaps extension, of the efficacy of current and future antibiotics.
- A strengthened surveillance system that utilizes novel diagnostics to track pathogen resistance.
- Better clinical decision-making that rapidly treats infections, prevents new infections and encourages antibiotic stewardship through use of antibiotics appropriate for a specific infection.



- A reduction in total or overall healthcare system costs, illness, hospitalization and deaths.

While the GAIN Act has begun to stimulate some development, there is still a need for broader regulatory options that will help with alternative trial endpoints and innovative trial design. Additionally, there is a significant need for increased government funding of basic research and building of partnerships with industry in developing new medicines. Finally, reimbursement reforms that will encourage companies to invest in new antimicrobials and enabling diagnostics are important and necessary. In addition to existing antibiotics, novel focused-spectrum biological anti-infective platforms for antibodies and vaccines could be successfully used to develop new approaches to prevent or treat resistant infections, thus allowing the public health systems to potentially reduce drug resistance and preserve the current and future antibiotics for therapy when actually needed.

To best leverage these new platforms, both programs and incentives will be needed to encourage the private sector to invest in new drug and biological approaches for targeting bacterial pathogens. Over the last decade, antibiotics, antibody and vaccine developers have found it very difficult to garner interest from both private investors and large biopharmaceutical companies in the development of novel approaches for infectious diseases. For their part, large biopharmaceutical firms must continuously justify investments in antibiotics and other infectious disease products against other therapeutic areas with a greater potential return on investment (ROI).

Expanding the incentives for the development of new antibiotics to novel infectious disease prophylactic and treatment modalities including novel vaccines and antibodies could positively impact the treatment and prevention of many of the illnesses caused by antibiotic resistant pathogens.

IV. PROPOSAL

BIO proposes a set of regulatory, funding and reimbursement incentives for developers of drugs, biologics, vaccines and diagnostics to help increase the number of products available for the most important resistant bacterial pathogens.

Development:

- Make changes to the GAIN Act that include similar incentives for novel biologics (e.g., antibodies), preventive approaches, treatments and vaccines that are targeted to the same qualified infectious disease pathogens identified by the CDC and the FDA.
 - Apply the incentives of the GAIN Act (and the proposed ADAPT Act to novel vaccines, antibodies and other new biological based modalities to treat and prevent infectious diseases.



- Designate all investigational products that address one or more of the pathogens identified by the CDC as urgent, serious or of concern as “breakthrough” products to help ensure high-level FDA management and engagement.
 - Require the FDA to seek input from outside thought-leaders on the best, non-product specific evidentiary standards that can be included in guidance from the Agency.
 - Require FDA to provide timely input during the development cycle for QIDP products.
- Support the ADAPT Act, especially provisions that will help with the development and use of alternative trial endpoints and other pathways that accelerate clinical trials and approvals.
 - Propose a set of research incentives that lead to the development of novel diagnostics, as they are vital to the development of antimicrobials needed for better clinical decision-making and judicious antibiotic use.
 - Support efforts to harmonize international regulatory procedures, especially between the FDA and the European Medicines Agency (EMA), in terms of trial requirements and other clinical trial design issues in order to speed approvals for high value antibiotics, treatments and vaccines.
 - Expand the use of Priority Review Vouchers to those products that address the CDC threat list where there is a dual-use for the product as a medical countermeasure (MCM) by the Biomedical Advanced Research and Development Authority (BARDA).
 - Support novel economic models that encourage innovation by de-linking a reliance on sales volume as the key driver for economic returns.

Funding:

- Increase the use of Other Transactional Authority (OTA) by BARDA as a way of driving collaborative promotion for special products.
- Expand the scope of BARDA's mandate to include investment in topical antibiotics that treat resistant pathogens as well as specific vaccines for QIDP pathogens, as appropriate.
- Expand the scope of the Defense Advanced Research Projects Agency (DARPA) to include partnerships with industry on novel antibiotics, monoclonal antibiotics, vaccines, preventive treatments and diagnostics.



Delivery Incentives:

- Support DISARM Act provisions that help provide sufficient and predictable payments for both novel drug and biological antimicrobials that prevent costly infections or are curative and life-saving.

Incentivizing Biomedical Innovation

The process of developing new medicines for patients in need is expensive and time-consuming. Over the past several decades, the time and cost to develop a new medicine have increased. The biopharmaceutical industry is one of the world's most research-intensive industries, spending tens of billions of dollars each year on research and development (R&D) aimed at improving the lives of people across the globe. On average, it now costs more than \$1 billion to develop each new drug (with some estimates much higher), and takes more than a decade between discovery and approval. In contrast, costs for drug development were approximately 600 percent less in the 1970s than in the 2000s according to one estimate,¹ while development timelines for new medicines have expanded from six years in the 1970s to 13.5 years in the 2000s.²

There are, of course, a variety of factors that contribute to this growing problem – including the inherent iterative and unpredictable nature of scientific development, high discovery and development attrition rates, and lengthy and complicated regulatory processes.³ Through its 21st Century Cures Initiative, the House Committee on Energy and Commerce is highlighting the importance to the public health of improving this paradigm, and is working to address many aspects of the drug discovery, development, and delivery processes in an effort to help get innovative medicines to patients faster.

BIO encourages the Committee, as part of its 21st Century Cures Initiative, also to consider ways to enhance current incentives to spur further innovation and scientific advancement in drug development. In particular, the concept of regulatory exclusivity has long been recognized as one that advances innovation and promotes the development of medicines—or new indications for existing medicines—that otherwise might not be developed due to scientific, regulatory, financial, or intellectual property-related challenges that disincentivize sufficient levels of investment. For example, it is well accepted that R&D into many potentially promising molecules is often shelved because the lack of adequate remaining patent life or concerns about the strength or enforceability of existing patent protection make relying on current levels of regulatory exclusivity alone economically infeasible.⁴ Similarly, there is under-investment in R&D aimed at some of our most intractable and expensive public health challenges, such as Alzheimer's and diabetes, due to the scientific difficulties and lengthy regulatory requirements involved in such development programs – both of which cause existing incentives to be inadequate.

Regulatory exclusivity encourages innovators to invest the resources and time necessary to conduct the complex development work required to prove a new medicine is safe and

¹See summary of UK study in Burrell Report, *New Estimate of Drug Development Costs Pegs Total At \$1.5 Billion*, (Dec. 2012), available at http://www.burrillreport.com/article/new_estimate_of_drug_development_costs_pegs_total_at_1_5_billion.html

² Id.

³ As noted by the NIH's National Center for Advancing Translational Sciences, "One drug typically involves the investigation of up to 10,000 compounds and takes about 14 years to be approved." See <http://www.ncats.nih.gov/research/reengineering/process.html>. Further, an analysis conducted by *Forbes* found that approximately 95 percent of all drugs researched for use in humans do not make it all the way through to FDA approval. See <http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/>

⁴ Ben Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 *Texas L. Rev.* 503, 545 (2009)

effective and to secure regulatory approval of that new product. Data protection in particular does so by requiring third parties seeking to gain approval of a same or similar product either independently to generate the full range of pre-clinical and clinical evidence for their own product or to wait a limited period of time before seeking approval via an abbreviated pathway, based on the innovator's years of technical and financial investment. Data protection thus prevents parties from prematurely benefitting from the investments and efforts made by the innovator to secure original approval of its product and helps to ensure that the innovator can receive a return on its investment prior to generic or biosimilar competition.

BIO encourages the Committee to consider ways to enhance existing incentives such as regulatory and patent-related protections to better address the challenges sought to be overcome by its ambitious 21st Century Cures Initiative.

Improving Scientific and Medical Dialogue to Enhance Patient Care

I. Summary

Improve the medical and scientific dialogue on the most effective patient care by removing certain limitations on the ability of biopharmaceutical manufacturers to communicate with health care professionals and payor representatives concerning truthful and not misleading information about approved uses or medically accepted alternative uses of approved products.

II. Background

It is common, legal and appropriate for doctors to prescribe approved medicines for a variety of uses, some of which may not be included within the product label or covered by the approved indications.¹ Indeed, it may be unethical for physicians (or other health care professionals) not to do so, as alternative uses of approved medicines may reflect the standard of care. As noted by Gregory Schimizzi, M.D., in his testimony before the House Health Subcommittee Hearing on Barriers in Health Communication, “[M]any non-approved indications can be found in standard textbooks of medicine and surgery in all specialties and subspecialties for patients of all ages and are the generally accepted standard of medical care.”² Standards and medical approaches to patient care evolve and iterate constantly, as health care professionals seek to find the best way to care for and treat their patients, and this evolution is fully present in the area of medicines. Indeed, as articulated by Health Subcommittee Chairman Pitts at the same hearing, “Discovery of the risks and benefits of a drug or a treatment does not end with FDA approval or clearance. It is often just the beginning of learning about different usage for drugs and devices, for different indications, conditions and populations.”³ This evolution (and the benefits to patients that results) comes about through the critical learning that occurs in the sharing of scientific and medical information between and amongst health care professionals and other stakeholders in the healthcare ecosystem. A robust marketplace of scientific and medical dialogue leads to improvement in treatment approaches, and undoubtedly benefits patient care.

¹ For example, the American Medical Association’s House of Delegates Health and Ethics Policy on Patient Access to Treatments Prescribed by Their Physicians states “The AMA confirms its strong support for the autonomous clinical decision-making authority of a physician and that a physician may lawfully use an FDA approved drug product or medical device for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion; and affirms the position that, when the prescription of a drug or use of a device represents safe and effective therapy, third party payers, including Medicare, should consider the intervention as reasonable and necessary medical care, irrespective of labeling, should fulfill their obligation to their beneficiaries by covering such therapy, and be required to cover appropriate “off-label” uses of drugs on their formulary.” See AMA House of Delegates Health and Ethics Policies, H-120.988 Patient Access to Treatments Prescribed by Their Physicians. <https://ssl3.ama-assn.org/apps/ecom/PolicyFinderForm.pl?site=www.ama-assn.org&uri=%2fresources%2fhtml%2fPolicyFinder%2fpolicyfiles%2fHnE%2fH-120.988.HTM>.

²Testimony of Gregory Schimizzi, M.D, House Energy and Commerce Subcommittee on Health Hearing on Barriers in Health Communication, July 22 2014. Dr. Schimizzi, as of the date of his testimony, was a member of the Board of Directors and past president of the Coalition of State Rheumatology Organizations or CSRO, and a private practice rheumatologist at the Carolina Arthritis Associates and Wilmington, North Carolina.

³House Energy and Commerce Subcommittee on Health Holds Hearing on Barriers in Health Communication, July 22, 2014. Introductory Statement by Health Subcommittee Ch. Pitts.

The ongoing scientific and medical dialogue about what may be beneficial for patients generally (or for individual patients in specific instances) needs to occur in an active, iterative, and expansive information marketplace. However, drug manufacturers—who generally know the most about their own drugs—currently are limited in their participation in this dialogue, thus artificially narrowing the distribution and flow of relevant medical or scientific information to physicians, nurses, payor representatives, or other relevant contributors to patient care. Every other party in the healthcare ecosystem (physicians, healthcare professionals, patients, payor representatives, public media, on-line discussion fora) may participate in this dialogue without FDA limitation, despite the fact that these other parties may not be aware of the most accurate or up-to-date information. This is because FDA’s current interpretation generally restricts or limits certain manufacturer proactive communication of even truthful and non-misleading scientific or medical information about the manufacturer’s approved product, if such information is not included within the approved product label. This is true even if information is presented solely to physicians or other appropriately qualified healthcare professionals, and further even if such alternative uses reflect the current accepted standard of care or are otherwise medically accepted uses.

The current restrictive environment limits valuable medical and scientific dialogue. As articulated by Dr. Schimizzi at the same July 22 hearing, “The FDA does not allow pharmaceutical companies to actively distribute key clinical information, even if it is related to the on-label indication unless it is explicitly referenced in the package insert of that product. By limiting the sharing of information, physicians are hampered in their ability to gain all of the firm scientific rationale and medical evidence needed to treat patients.”⁴ Indeed, as noted by Subcommittee Chairman Pitts in his opening remarks to this hearing, “Treatment in the real world also brings out additional information on safety and efficacy, and ensuring that this knowledge is shared widely among providers, patients and researchers is critical. As a result, the ability of patients, physicians *and developers* to communicate effectively is so important for the future of cures in this country” (emphasis added). Well-informed health care professionals benefit patient care and improve outcomes, and an important component of this education should be effective communication of medical and scientific information with, by, and between the developers of medicines and healthcare professionals.

In addition, improving scientific and medical dialogue by removing FDA’s overly broad limitations on manufacturers’ proactive distribution of truthful and non-misleading medical or scientific information on approved products, including medically accepted alternative uses of such products, is more consistent with First Amendment principles and recent case law. Indeed, in the recent Supreme Court decision in *Sorrell v. IMS*, in which the Court addressed the constitutional protection for pharmaceutical manufacturer communications,⁵ the Court reiterated the importance of the free flow of information to informed decision making. Specifically, the Court stated,

⁴ Testimony of Gregory Schimizzi, M.D., Health Subcommittee Hearing, July 22, 2014.

⁵ In the *Sorrell* case, the Supreme Court invalidated a Vermont law that purported to prohibit pharmaceutical companies from using certain types of data in speaking to healthcare professionals about their drugs; yet the law allowed anyone other than a pharmaceutical company to use the same data in speaking about the same drugs. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011), The Court rejected laws that discriminate in that fashion based on the content of the speech or the identity of the speaker. The Court also held that “[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment,” and that the Vermont law was “presumptively invalid” because it would “impose a burden based on the content of speech and the identity of the speaker.” *Id.*, at 2659.

As one Vermont physician put it: ‘We have a saying in medicine, information is power. And the more you know, or anyone knows, the better decisions can be made.’ There are similar sayings in law, including that ‘information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.’ The choice ‘between the dangers of suppressing information, and the dangers of its misuse if it is freely available’ is one that ‘the First Amendment makes for us.’⁶ [citations omitted].

FDA’s current regulatory and enforcement framework regarding the communication of medical and scientific information is constitutionally suspect and impedes important public health benefits that may result from free and open scientific and medical dialogue. Since millions of patients are actively and appropriately treated with medically-accepted alternative uses of medicines (including a significant proportion of oncology treatments), patients deserve to know that health care professionals and payor representatives can receive truthful and not misleading medical or scientific information about these uses proactively from the companies that researched, developed, and delivered these medicines.

III. Proposal

This 21st Century Cures proposal would enhance beneficial healthcare communication and update the regulation of healthcare communication consistent with our 21st century healthcare system, and is consistent with First Amendment principles and case law.⁷

The proposed legislation would:

- First, enhance public health by reaffirming that manufacturers of medicines can freely provide to healthcare professionals and payor representatives truthful and not misleading information about FDA-approved or medically-accepted but unapproved uses of their medicines – just as payors, the U.S. government, and all other participants in the healthcare system now do.
 - The proposed legislation would only apply to information about FDA-approved uses or medically accepted alternative uses of approved medicines.
 - Medically accepted alternative uses are those uses that are based on sound scientific evidence and sound medical opinion (as recognized by the medical community in generally accepted compendia or clinical practice guidelines), and covered or reimbursed by payors such as federal health care programs or private insurers.
- Second, the proposed legislation also would make clear that the Food Drug & Cosmetic Act does not permit enforcement action based on the subject matter of a person’s truthful, non-misleading communication or the identity of the speaker. This approach is supported by, and consistent with, recent case law.

⁶ Id., at 2671.

⁷ This proposal addresses specific aspects of manufacturer product communications pertaining to truthful and not misleading communication about approved uses and medically accepted alternative uses of approved products. We note that there are other important aspects of FDA limitations on manufacturer product and related communications that are not addressed by this proposal and that are the subject of ongoing debate, dialogue, and in some cases legal challenge and/or regulatory processes and procedures.

- Third, the proposed legislation would define “truthful and non-misleading” communication consistently with the Lanham Act standard, which has been used by courts to define false or misleading advertising for almost 70 years, and would include an analysis of the appropriate context and/or medically or scientifically relevant assumptions and caveats.
 - Such non-misleading and truthful information could include observational data and real world evidence, pharmacoeconomic information, meta-analyses, and other valuable types of information about medicines that are not generated from two adequate and well-controlled clinical trials yet may help improve patient care.



FDA Scientific Infrastructure, Management, and Human Capital

I. SUMMARY:

In order to realize a vision of a 21st Century regulatory environment, it is fundamental to enhance FDA's scientific capacity and infrastructure. This can be achieved by promoting the Agency's ability to attract and retain scientific and technical experts, enhancing FDA's institutional management processes and expertise, and improving FDA access to adequate funding and resources.

II. BACKGROUND AND PROBLEM STATEMENT

As one of the nation's preeminent science-driven public health agencies, it is critical that FDA have the scientific infrastructure, staff capacity, and institutional management processes necessary to carry out its mission, particularly with respect to the development and review of innovative modern therapies that can advance patient care.

A. Staffing and Strategic Human Resources

FDA's capacity to recruit and retain high caliber staff has been a long-standing issue. As stated by FDA's own Science Board in 2007:

*"FDA's failure to retain and motivate its workforce puts FDA's mission at risk. Inadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or, even worse, the wrong decision on regulatory approval or disapproval. During our encounters with staff and center leadership, we were struck by the near unanimity that the shortage of science staff (due to lack of resources to hire) and the inability to recruit and retain needed expertise are serious, longstanding challenges."*ⁱ

From the Commissioner down to the review divisions, FDA must articulate a mission and environment that attracts and motivates highly skilled staff and promotes excellence and accountability. To prepare FDA for the future, the Agency must be able to recruit and retain high-caliber, dynamic managers and scientists. FDA has cited two key hiring challenges in recent months: filling senior-level management vacancies and meeting user fee program hiring targets.

1. Recruitment and Retention

A number of high profile departures over the last eighteen months have left an unprecedented number of senior-level vacancies.ⁱⁱ These senior managers, who are positioned directly below FDA's political and career leadership, play a crucial role in managing FDA review and policy operations, promoting accountability, and implementing new initiatives. FDA is also facing the looming retirements of several key CDER leaders, and a potential wave of retirements across the agency's review divisions has focused attention on the Agency's limited succession planning for these departures and the perception that

FDA lacks a sufficiently “deep bench” of managers being groomed for these positions. FDA has also faced challenges in luring qualified staff with management experience from the private sector and academia to fill these positions.

In addition, under PDUFA V FDA was required to hire 129 new scientists, biostatisticians, and technical experts to staff priority regulatory science activities, including biomarker and PRO qualification, rare disease drug development, meta-analysis and enhanced communication. The hiring freeze due to the FY13 sequestration postponed the hiring of these staff, but limited progress has been made towards meeting these hiring goals since the sequester was lifted and the user fee resources were restored.

2. Human Resources Strategies

The obstacles that FDA faces are in many cases structural and the result of both Department of Health and Human Services and Federal Government hiring practices and processes. For example, FDA Human Resources systems have proven to be suboptimal. During the prior Administration, all HHS HR offices were consolidated within HHS, which exacerbated hiring problems. Just last year FDA's HR office was returned to the Agency and is still in the process of ramping up. Often, hiring a new staff member can take upwards of six months, during which a competitive candidate may accept employment elsewhere.

Other Federal Government-wide hiring practices have undermined FDA's ability to hire the most qualified recruits. Under the "Rule-of-Three," potential candidates are numerically ranked depending on a number of factors which are often unrelated to the specific position in question. Only the three top scoring candidates will be presented to the hiring manager. A qualified candidate below the top three scoring applicants may not be presented for the position unless a higher scoring applicant declines or is appointed to the position, thereby “burying” other qualified candidates in the HR system.

FDA has been able to circumvent these rules by utilizing Direct Hiring Authority granted by the Office of Personnel Management in 2008. This exception only applies to rank and file positions (GS1-GS15), not Senior Executive Service (SES) positions, a separate pay scale for senior level managers and executives and where most key FDA vacancies exist. Members of the SES serve in the key positions just below the top Presidential appointees. SES members are the major link between these appointees and the rest of the Federal work force.

FDA has also noted that Federal Government pay-scales have limited its ability to recruit top-tier managers, especially since many qualified candidates would have to take a pay-cut to join FDA. Even under the more generous Senior Executive Services pay scale, compensation may be functionally capped at levels that are too little to compete with senior private sector management positions.

Title 42 allows HHS to appoint specialists, some of whom have special training or qualifications, and pay them more closely in line with what they might earn in the private sector. FDA and other agencies have been granted additional flexibility under Title 38 and Title 42 authorities to quickly fill gaps in medical expertise to advance research and persons to public health emergencies. HHS witnessed significant growth in Title 42 hires in recent years, and the Administration has cracked down on the practice making it bureaucratically difficult to authorize a new Title 42 compensation level. While FDA retains Title 42 authority, other agencies, including NIH and CDC, have been afforded greater flexibility in applying Title 42 authorities and have been able to utilize it more effectively. Other

Agencies, such as the Securities and Exchange Commission, have been granted the explicit authority to set compensation for specialists at levels comparable with the private sector.ⁱⁱⁱ

3. Professional Development:

Furthermore, recent restrictions on FDA's ability to attend scientific conferences and standard-setting meetings have hindered the ability of staff to keep pace with advancements in biomedical science. These limitations negatively impact staff morale and the ability to attract new scientists to the Agency.

B. External Scientific and Technical Advice

Additionally, in emerging scientific fields and areas where FDA does not have adequate internal expertise, it is also important that FDA have appropriate processes in place for accessing external scientific advice.

For example, the Food and Drug Safety and Innovation Act of 2012 (FDASIA) expanded FDA's authority to consult with external experts on rare diseases, targeted therapies, and genetic targeting of treatments to a broader range of conditions. FDA would benefit if this authority were utilized more effectively and expanded to other areas of specialized expertise.

Additionally, despite the best intentions in the conduct of Advisory Committee meetings, there remain inconsistencies in the conduct of effective discussions across the FDA review divisions. These inconsistencies can be traced to challenges in the ability of the agency to identify and recruit individuals with the appropriate scientific expertise to address challenging and complex topics. In addition, sponsors report inefficiencies in communications between the agency and industry during the preparation and actual conduct of Advisory Committee meetings, which can confuse the issues and otherwise divert attention from the salient issues to be considered by the advisory committee members.

C. Institutional Management and Governance

The FDA is a large, complex organization. The substantial size of FDA presents a challenge to Agency leadership. FDA consists of six product centers, one research center, and two offices. It employs over 11,500 full time equivalent (FTE) staff across the world. The Agency is responsible for regulating more than \$2 trillion in food, drugs, medical devices, cosmetics, dietary supplements, and other consumer goods—nearly a quarter of the U.S. consumer goods supply. The size and complexity of the FDA, increasing statutory responsibilities, and globalization of FDA-regulated industries have placed significant demands on FDA and may have hampered its ability to pursue forward-looking management strategies to prepare for the future of biomedical science.

1. External Management Review Board:

Congressman Gingrey (R-GA) has proposed the establishment of an external Regulatory Science Implementation and Management review Board through the "Patient Access Reform Act of 2011." The establishment of an external Management Review Board could help identify deficiencies in FDA's management and organizational structures that threaten the Agency's ability to meet its numerous regulatory responsibilities. The Board, consisting of experienced external advisors, could conduct periodic reviews of FDA's management and

organizational structure to provide fresh, visionary, and independent thinking, and its recommendations on how to improve FDA's ability to fulfill its mission could help the Agency address key operational challenges.

The creation of a management review board to advise an agency on management and organizational issues is not unprecedented. For example, the National Institutes of Health (NIH) Reform Act of 2006 established a Scientific Management Review Board (SMRB) to advise the NIH Director and other appropriate officials on the use of certain statutory authorities to reorganize NIH to carry out its activities more efficiently. The NIH SMRB helps to ensure that NIH's structure is optimal for supporting the advancement of science.

2. Governance and Quality Management Systems:

The FDA's stated fundamental guiding principles include: science-based decision making, innovation/collaboration, transparency, and accountability.^{iv} Management tool solutions should be considered that assist the Agency in achieving its stated objectives.

While the FDA has made some of the above principles a priority in recent years, the Agency has not broadly instituted a management process that explicitly defines, measures, analyzes, improves, controls, and validates key processes utilized by its scientists as decisions are made.

Quality system processes and controls are the backbone of a consistent and efficient FDA drug review system – and are arguably more important to a well-run FDA drug review process than one-off improvements. Furthermore, without a quality system in place, it is difficult to even ascertain the impact of one-off improvements. Tying a quality system back to the FDA guiding principles outlined above would provide the Agency with a key management tool that could help protect and advance the public health by improving efficiency, predictability and consistencies of drug review decisions and Agency advice to sponsors. It could both improve operational effectiveness and provide the Agency greater confidence that processes will more routinely ensure quality outcomes.

Recognizing this fact, the FDA has prioritized the development and implementation of such a quality system in several different initiatives—including its most recent strategic plan. A stated FDA goal is to maintain a culture of continual business process improvement which strengthens the overall operation and effectiveness of FDA.^v As the FDA continues to evolve, patients expect a regulator that is consistent from one decision to the next and reliable across FDA review divisions—using standardization and repeatable processes so that an innovator clearly understands the regulatory requirements and institutional learning can be harnessed.

III. PROPOSALS:

A. Enhance FDA's Ability to Recruit and Attract Qualified Candidates

- Provide FDA with flexibility to set salary levels commensurate with the private sector, similar to authority granted by Congress to the Securities and Exchange Commission. Alternatively, establish salary waivers for the five most senior Agency staff, not including political appointees.

- Grant FDA Title 42 authority on par with NIH and reduce bureaucratic barriers to authorizing Title 42 hires. This could be achieved by directing the Department of Health and Human Services to identify the types of scientific, technical, and managerial positions that would be eligible for hire under Title 42. A similar HHS memorandum governs NIH Title 42 hiring and preserves flexibility within the framework of the Title 42 authority.^{vi}
- Expand Direct-Hiring Authority to Senior Executive Services positions.

B. Professional Development

- Remove barriers to FDA travel to scientific conferences and technical standards-setting meetings.
- Require FDA to establish a formal succession plan for senior-level employees, which would include staffing contingency plans and training / professional development for prospective senior management positions.

C. Access to External Scientific and Technical Expertise

- Broaden FDA's ability to seek scientific expertise from qualified external experts and technical professionals. Expand FDA's §903 authority to consult with external experts on rare diseases, targeted therapies, and genetic targeting of treatments to a broader range of conditions and provide mechanisms for sponsors to request consultation during drug development and review.
- Furthermore, direct the Agency to initiate an assessment on the performance of the overall advisory committee process and supporting systems to identify additional areas of potential improvement. The assessment should identify barriers to the conduct of advisory committee meetings that are both highly effective and reflective of the best expertise that is available. This initiative should include public release of the assessment report with public comment, and subsequent public hearings to gain viewpoints from all stakeholders.

D. FDA Regulatory Science Implementation and Management Review Board

- Establish a FDA Regulatory Science Implementation and Management Review Board to incorporate and leverage knowledge from governmental agencies, patient organizations, academic institutions, medical research experts, and industry to provide FDA with information that would ensure timely and effective review of innovative treatments and therapies.

BIO is pleased to provide the following feedback on the "Patient Access Reform Act of 2011" sponsored by Congressman Gingrey.

i. Implementation Mechanism:

Similar to the NIH Management review board, there should be a formal mechanism to ensure that the recommendations are responsibly implemented in a timely manner. *Within*

100 days of issuing a report, FDA shall begin to implement the recommendations made by the Board, except when the Commissioner objects to any recommendation or if Congress passes a joint resolution overriding the recommendation.

ii. *Stakeholder Representation:*

Composition of the board should include FDA leadership, management optimization experts, individuals with experience managing complex scientific organizations, industry, patients, and academia. Under the Gingrey proposal the Board would consist of the following representatives:

- FDA Commissioner (or designee)
- 2 additional FDA representatives
- 1 CDC representative from either the Office of Infectious Disease or Associate Director for Science
- 1 DARPA representative
- 2 NIH representatives
- 2 non-profit entity representatives
- 3 patient advocacy representatives
- 3 medical research entity representatives
- 5 industry representatives
- 2 venture capital representatives

BIO suggests clarifying that the industry representatives will include 3 biopharmaceutical representatives and 2 small biotechnology company representatives (defined as less than 250 employees) with appropriate expertise relevant to the Board and subcommittees.

iii. *Board Committees:*

The Board would have 4 Committees that it would work with to establish research priorities and meet deadlines for required reports:

- The Regulatory Review Committee
- The Scientific Review and Advisory Committee
- The Patient Access Improvement Committee
- The Management Review Committee

We suggest that the proposal provide more directive as to what types of analysis and activities should be done by the Committees such as the following:

The *Regulatory Review Committee* should examine and engage with governmental agencies, public private partnerships, medical researchers, industry and patient advocacy organizations that are or have conducted research on the utilization of novel clinical or surrogate endpoints, modern clinical trial designs and modern clinical development tools including but not limited to diagnostics. The biannual report should include information on these research activities and make recommendations to FDA on how to enable utilization of novel clinical/surrogate endpoints and modern approaches.

The *Scientific Review and Advisory Committee* should examine and engage with governmental agencies, public private partnerships, medical researchers, industry, and patient advocacy organizations about emerging biomedical technologies and novel approaches to clinical development in the early stages of research. The biannual report should include information on these medicines and approaches and make recommendations on how to ensure the FDA regulatory process will be prepared to enable effective clinical development and review processes for such medicines and approaches.

The *Patient Access Committee* should examine and engage with governmental agencies, public private partnerships, medical researchers, industry and patient advocacy organizations that are or have conducted research on, including but not limited to, the development of clinical registries, patient reported outcomes, patient centric benefit-risk assessments, and development of clinical trial networks. The biannual report should include information on these research activities and provide recommendations about how these activities could be better coordinated, leveraged and utilized by industry and medical researchers to better ensure patient perspectives are integrated into the drug development and review process.

The *Management Review Committee* should examine and engage with governmental agencies, public private partnerships, medical researchers, industry, and patient advocacy organizations about the review and approval of FDA-regulated medical products, including drugs, biologics, and medical devices. The biannual report should include information on FDA review performance, FDA review management processes, consistency in review procedures across offices and review divisions, and the incorporation of new technologies and scientific methodologies to support regulatory decision-making.

iv. FDA Feedback on Board Recommendations

We suggest that FDA hold a public meeting or issue a document to provide information on why recommendations will or will not be advanced.

v. Duplication of Effort:

The Board should ensure that there is no duplication of effort and make recommendations regarding existing FDA boards and advisory groups that may be doing duplicative/similar work, including the FDA Science Board.

E. FDA Quality Management and Continuous Process Improvement System

- Establish a quality management system at the FDA which explicitly defines, measures, analyzes, improves, controls, and validates key processes utilized by its scientists as decisions are made. A stated FDA goal is to maintain a culture of continual business process improvement which strengthen the overall operation and effectiveness of FDA^{vii}. As the FDA continues to evolve, standardization and repeatable processes are important so that an innovator clearly understands the regulatory requirements and institutional learning can be harnessed. Tying an improved process improvement system back to the FDA guiding principles would provide the agency with a key management tool that could help protect and advance the public health by improving the transparency and efficiency of drug review decisions.

F. Ensure Adequate FDA Appropriations and Financial Resources:

- Continue to support FDA through the annual appropriations process to ensure that Agency resources keep pace with FDA's expanding responsibilities, modern scientific advancement, and the complexity of FDA-regulated products.

References:

- ⁱ FDA Science Board, *FDA Science and Mission at Risk*, November 2007, http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_fda%20report%20on%20science%20and%20technology.pdf
- ⁱⁱ Pink Sheet, *FDA Searches Small Industry Candidate Pool To Fill Executive Vacancies*, March 24, 2014, <http://www.pharmamedtechbi.com/Publications/The-Pink-Sheet/76/12/FDA-Searches-Small-Industry-Candidate-Pool-To-Fill-Executive-Vacancies?result=8&total=38&searchquery=%253fq%253dmoscicki>
Deputy Director of the Office of New Drugs, Director of Medical Policy, Director of the Office of Generic Drugs, Chief Scientist, and Senior Counselor to the Commissioner
- ⁱⁱⁱ **§4802. Securities and Exchange Commission**
- (a) In this section, the term "Commission" means the Securities and Exchange Commission.
- (b) The Commission may appoint and fix the compensation of such officers, attorneys, economists, examiners, and other employees as may be necessary for carrying out its functions under the securities laws as defined under section 3 of the Securities Exchange Act of 1934 (15 U.S.C. 78c).
- (c) Rates of basic pay for all employees of the Commission may be set and adjusted by the Commission without regard to the provisions of chapter 51 or subchapter III of chapter 53.
- (d) The Commission may provide additional compensation and benefits to employees of the Commission if the same type of compensation or benefits are then being provided by any agency referred to under section 1206 of the Financial Institutions Reform, Recovery, and Enforcement Act of 1989 (12 U.S.C. 1833b) or, if not then being provided, could be provided by such an agency under applicable provisions of law, rule, or regulation. In setting and adjusting the total amount of compensation and benefits for employees, the Commission shall consult with, and seek to maintain comparability with, the agencies referred to under section 1206 of the Financial Institutions Reform, Recovery, and Enforcement Act of 1989 (12 U.S.C. 1833b).
- (e) The Commission shall consult with the Office of Personnel Management in the implementation of this section.
- (f) This section shall be administered consistent with merit system principles.
(Added Pub. L. 107–123, §8(a), Jan. 16, 2002, 115 Stat. 2398.)
- ^{iv} Strategic Priorities 2011-2015, Responding to the Public Health Challenges of the 21st Century, United States Department of Health and Human Services, Food and Drug Administration
- ^v Strategic Priorities: 2011-2015, Department of Health and Human Services, United States Food and Drug Administration, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM252092.pdf>
- ^{vi} NIH IMPLEMENTATION OF THE NEW HHS TITLE 42 (f) POLICY, June 27, 2005
<http://sourcebook.od.nih.gov/administrative/title42%28f%29implementation.htm>
- ^{vii} Strategic Priorities: 2011-2015, Department of Health and Human Services, United States Food and Drug Administration, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM252092.pdf>

STIMULATING INNOVATION IN VACCINES FOR U.S. AND GLOBAL HEALTH

I. SUMMARY

For more than a century, vaccines have been one of the most significant public health interventions around the world. During the early 2000s, the United States saw a dramatic increase in the number of new vaccines introduced, especially for the pediatric and adolescent populations. Many of these vaccines were also introduced in other countries, including in emerging and developing markets. Yet there are still important infectious diseases, such as respiratory syncytial virus (RSV), malaria, human immunodeficiency virus (HIV) and tuberculosis (TB), which have long been top priorities for global vaccine development. In addition, emerging infectious diseases, such as Ebola, and bacterial diseases that have become antibiotic-resistant are areas where vaccine development could have a significant impact.

The availability of novel vaccines for all ages could have a significant impact on unmet medical needs with high value for the healthcare system and for society in general. Biotechnology and pharmaceutical companies that develop and manufacture vaccines face unique challenges in discovery, development, and delivery.

This paper discusses challenges surrounding vaccine development and lays out a proposal for targeted activities that could incentivize increased R&D into new vaccines for both the U.S. and global health.

II. BACKGROUND

Public health has greatly improved due to the broad use of multiple safe and effective vaccines across the lifespan. Indeed, vaccines are unique in that more benefits accrue to more people the more they are used. Given the nature of infectious diseases, immunization of large populations protects not only the individual but many of those who come into contact with that individual, thus benefiting the broader community. The Centers for Disease Control and Prevention (CDC) estimates that the vaccination of children in the United States between 1994 and 2013 will

- Prevent 322 million illnesses;
- Help avoid 732,000 deaths; and
- Save nearly \$1.4 trillion in total societal costs, including \$295 billion in direct healthcare costs.

This is just data for the pediatric population, where we have the highest immunization rates as a nation. There are additional cost-savings in the prevention of vaccine-preventable diseases in adults, and the elderly, especially among the vulnerable Medicare population.

In the late 1970s and early 1980s, many companies were exiting the vaccine business because of market size uncertainty and liability pressures. However, over the following



decade, positive changes in the landscape encouraged manufacturers to introduce new vaccines:

- Congress and the vaccine community created the Vaccine Injury Compensation Program (VICP), which helped decrease liability risks for manufacturers and providers;
- New vaccine technologies, such as recombinant technology, virus-like particles and conjugation led to innovations in several very important disease areas;
- Recent increased interest in vaccinating specific at-risk populations created new vaccine immunization platforms, including one focused on maternal immunization; and
- The Vaccines for Children (VFC) program and the accompanying Advisory Committee on Immunization Practices (ACIP) process provide an evidence-based recommendation process that defined the public sector market while overtly maintaining the commitment to a private market, especially for the essential pediatric and adolescent populations.

These events helped encourage renewed investment in novel vaccines. During the early 2000s, the United States saw a dramatic increase in the number of new vaccines launched for children, adolescents and adults. New vaccines to protect against pertussis, rotavirus, human papilloma virus (HPV), pneumococcal bacteria, certain types of meningococcal infection, shingles and unique approaches to influenza vaccines were made available in the United States, Europe and many emerging and developing countries. Smaller biotechnology companies and some large pharmaceutical companies began to view vaccines as a viable area for increased R&D.

However, in recent years there have been numerous pressures on the U.S. and global vaccines environment:

- Consolidation of payers is causing downward pressure on prices and increased uncertainty for manufacturers;
- Several non-governmental organizations have advocated for broader access to pricing normally reserved for low-resource countries;
- Continuous policy activities at the state and federal levels in the U.S. are reducing the current and future value of the pediatric and adolescent vaccine markets (e.g., expansion of state vaccine financing programs, ACIP considerations of dose reduction policies);
- Regulatory requirements and complexities have increased due to the need to use novel and more complex technologies, which may lead to larger clinical trial sizes; and
- Investors have shifted capital to companies developing orphan or cancer drugs due to strong market potential for these therapies.

Even though we currently have a suite of excellent, safe, and effective vaccines in the United States, there is still more that could be done. Both large and small vaccine companies are working on new and vitally important vaccines in many areas where



there is significant unmet medical need in both developed and developing countries. A sustainable and dynamic research and development-focused vaccine industry is essential to bring many new vaccines to the global health community. Novel vaccines are needed in a broad array of areas, such as:

- Enhanced or optimized versions of existing vaccines for pertussis and influenza;
- Important diseases affecting children, adolescents and the elderly, such as RSV;
- Vaccines against healthcare-acquired infections (HAIs) that come from antibiotic-resistant bacteria, such as methicillin-resistant staphylococcus aureus (MRSA);
- Important global infectious diseases like TB, malaria and HIV; and
- Emerging infectious diseases such as Ebola, Marburg and the coronaviruses.

Concerning vaccine delivery, over the past decade many states and large counties have made significant investments in their immunization registries (Immunization Information System or IIS). Many of the IIS include vaccination information for children, adolescents, and adults but use varies by provider type and remains limited for those who see primarily adult populations. At the same time, growth of the information captured in electronic health records (EHRs) has created a unique opportunity to better characterize outcomes associated with vaccination.

III. PROBLEM STATEMENT

While vaccines have been successful in the past, the current healthcare and investment environments have increased the risks associated with developing new vaccines, and reduced the benefits. Even with the success of existing vaccine programs, small vaccine developers find it very difficult to garner interest from private investors and large biopharmaceutical companies, while large vaccine manufacturers must continuously defend their vaccine products against other therapeutic areas in their own organizations with greater potential return on investment (ROI).

The cost and complexity of developing new vaccines has increased dramatically over the last 10-15 years. Clinical trial sizes required are bigger and these trials must be done on a global scale. The demands for more safety data keep increasing, primarily as a way of addressing increased safety concerns from policymakers and the public. It is expensive and time consuming to build and maintain new manufacturing facilities for these complex biologics. Manufacturers often build these facilities while the vaccine is still in the clinical research phase, as the construction, inspection and approval of a new vaccine plant can take at least five years. For example, Sanofi Pasteur recently announced that they had already spent over \$1.7 billion on their global clinical research program and new manufacturing facility for their dengue vaccine candidate.

The decision to maintain a vaccine business or initiate research into a new vaccine has an opportunity cost. Companies must consider the benefit of using limited resources for a non-vaccine biologic or drug. In the past, the scientists, technologies and facilities used for vaccines were primarily applicable only to preventative vaccine development and manufacturing. As more companies invest in novel therapeutics that use the



immune system to treat chronic or non-communicable diseases (cancer, Alzheimer's, etc.) prophylactic vaccine-dedicated resources can more readily be repurposed to these new and growing therapeutic areas.

There is a need to stimulate research and development of new vaccines against important diseases affecting children, adolescents, adults and the elderly in the U.S., as well as for significant neglected tropical diseases (NTDs) and antibiotic-resistant bacterial diseases. For emerging infectious diseases and NTDs in particular, there is a need for significant public-private partnerships in order to reduce the risk of R&D for these vaccines. For many of these diseases, the vaccines will be used primarily in developing countries (e.g., malaria) or in countries responding to an emergency outbreak (e.g., Ebola). Therefore it is vital that processes, communication and funding be in place within the federal government as a vital partner in the development of these global public health interventions.

Even though vaccines against infectious diseases have a higher clinical success rate than therapeutic vaccines, investors view the ROI for other biologic products more favorably. Investors are concerned about several key issues with vaccines:

- There are high pre- and post-licensure safety requirements;
- There are limited large multinational vaccine partners for small biotechnology companies to partner with for assistance in getting through large Phase III clinical trials;
- The capital investment for manufacturing facilities is high;
- Funding for partnerships for neglected diseases and emerging global infections, especially from governments, has decreased;
- Some States in the U.S. have proposed using CDC federal contracts as a mechanism for purchasing vaccines for privately insured individuals, potentially eroding the discounts provided to the CDC for vulnerable populations; and
- Market conditions are shifting, including increasing uncertainty around the ACIP recommendation process.

While new vaccines are definitely needed, there are still some issues with access to existing vaccines, especially for adults, the elderly and persons living in underserved and rural areas. Although the U.S. has had strong ACIP recommendations for many adult vaccines for years, immunization rates remain woefully low. There are several reasons cited by vaccine stakeholders:

- Misunderstanding of the risk patients face from common infectious diseases means that many adults do not think they need to be vaccinated;
- Lack of a strong recommendation by a healthcare provider often reinforces the idea that vaccines for adults, even in high risk groups such as pregnant women, asthma and cardiovascular patients and the elderly, are not really necessary; and
- Complex reimbursement structure between Medicare Parts B and D leads to missed opportunities to vaccinate beneficiaries while they are in a physician's



office, while high and variable co-pays may place an undue financial burden on vaccinations given in the pharmacy setting.

IV. OPPORTUNITY

All of these challenges do not diminish the vital importance of preventing the spread of infectious diseases. In the United States, a better focus on the utilization of existing vaccines, especially within the systems that deliver vaccines to adults and the elderly, could have a significant impact on healthcare costs in the near term. Vaccine stakeholders within the National Adult and Influenza Immunization Summit (NAIIS) have specifically noted the need to greatly improve the interoperability and connection of traditional providers with community immunizers under the umbrella of the “immunization neighborhood.” Better connectivity and tracking between these disparate immunization providers could significantly increase vaccination rates in adults and build infrastructure that facilitates the introduction of new vaccines for both adult and maternal immunization in the future.

Other issues also provide a significant opportunity for the development of new vaccines. There are increasing issues in the United States and around the world with the growth of antibiotic-resistant pathogens and healthcare-acquired infections. The spread of many of these pathogens could be reduced or even eliminated with the application of a broad infectious disease strategy that strongly incentivizes the development of novel prophylactic and therapeutic vaccines. There are also numerous diseases, such as pertussis, influenza, RSV, norovirus, group B streptococcus and meningococcal infections which represent important unmet needs in the U.S. and many other countries. Diseases such as tuberculosis and HIV are global healthcare problems where vaccine development requires sustained partnerships between vaccine developers, non-governmental organizations and biotech firms to be successful. Lastly, there are still very important infectious diseases affecting huge populations in emerging and developing countries, such as malaria, Ebola and other NTDs. For many of these vaccines, especially those considered to be emerging infectious diseases, there is an opportunity to demonstrate a sustained commitment by the U.S. government to collaborative R&D for those vaccines where the government represents the primary or sole purchaser.

While there is active development of these and other novel vaccines, there is increasing uncertainty about the regulatory, recommendation, funding and reimbursement landscape for vaccines, especially in the United States.

V. PROPOSALS

BIO proposes a set of incentives for vaccine developers in terms of both development and delivery of vaccines to help reduce the complexity of the development process, reduce barriers to adoption of novel vaccines and increase access to adult immunizations. These proposals aim to create an environment that will support an increase in the number of preventive measures available for the most important pathogens affecting the U.S. and global healthcare systems.



DEVELOPMENT PROPOSALS:

A. FDA Guidance on Development of Vaccines that Target Emerging, Re-Emerging or Rare Infectious Diseases

Proposal: To facilitate the use of accelerated and expedited pathways for vaccines, propose that the Food and Drug Administration (FDA) issue formal guidance on vaccine development strategies to target emerging, rare or re-emerging infectious diseases, or infectious diseases where currently available vaccines are recognized as not meeting the full product profile desired by the public health community (e.g. pertussis vaccine). This includes the development of acceptable clinical and surrogate endpoints, guidelines on the use of novel adjuvants, the use of novel or accelerated study designs, use of observational real-world data, or demonstrating efficacy through challenge studies in healthy volunteers with the goal of establishing criteria for accelerated approvals.

Rationale: Companies have encountered significant challenges when developing vaccines for diseases that are either very rare or emerge unpredictably, as designing a clinical study can become untenable due to limited epidemiological data. In addition, there are diseases where optimized vaccines are of great interest to the vaccine community, such as pertussis or influenza, and where the development issues are more complex. FDA guidance would provide more direction to companies in these scenarios, which could positively impact the number of products in the pipeline.

B. NIH Programs to Support Translational and Clinical Phase Vaccine Research

Proposal: Propose sustainable funding programs at the National Institutes of Health (NIH) to help with translational and clinical phase vaccine research that fosters innovation and stimulates investor and biopharmaceutical company partnerships for later stage development.

Rationale: Many small biotech companies struggle to support vaccine research through phase 2. This proposal aims to address this through funding opportunities and a comprehensive set of resources for developers that support basic research, preclinical development, and clinical evaluation.

C. FDA Process to Expedite Issuance of Export Certifications for Vaccines

Proposal: Propose that FDA develop processes to expedite the release of U.S. manufactured vaccines for foreign countries that require a regulatory release from the country of origin.

Rationale: The ability to rapidly move vaccines between the U.S. and other countries is a vital step in reducing both regulatory approval cycles outside the country as well as



launch times for new products. This change would allow vaccine manufacturers to more readily export vaccines and decrease the time between manufacture and availability around the world.

D. Periodic Formalized Meetings Between CDC Immunization and Epidemiology Experts and Vaccine Developers

Proposal: Propose formalized meetings with CDC’s epidemiology and immunization program teams throughout the product development process to better understand the U.S. public health perspective as it relates to public health needs, epidemiology, implementation considerations and product profile to inform R&D planning.

Rationale: Public health needs, epidemiological data, and implementation considerations have not been consistently and clearly communicated by CDC to vaccine developers in the past. The creation of a more formal process for sharing important information between the federal government and vaccine developers could help increase clinical development efficiency as well as decreasing some of the uncertainty and risk of vaccine development, especially for those vaccines with more variable or shifting epidemiology.

E. Improvements to Tropical Disease Priority Review Voucher Program

Proposal: Propose that Priority Review Vouchers (PRVs) for neglected tropical diseases (NTDs) be harmonized with those for rare pediatric diseases in several aspects, such as allowing for unlimited transfers and a shorter notification period prior to PRV use (90 rather than 365 days). The proposal would also establish an FDA process for modifying/updating the NTD list at least every 5 years.

Rationale: NTD PRVs are currently subject to limitations that make them less attractive to investors as pull incentives than those for rare pediatric diseases. Further, eligible NTDs are currently codified in statute, which limits the agency’s ability to expand/modify the list of diseases as needed based on new epidemiological data, unforeseen outbreaks or increases in disease impact and/or stakeholder input. The proposal aims to make NTD PRVs more attractive as incentives and to allow for flexibility in terms of eligible diseases, while limiting expansion so as to not devalue PRVs by increasing the number available in the marketplace.

F. Updated FDA Guidance on Changes to an Approved Application for Biologics

Proposal: Propose that Congress direct the FDA to update the 1997 guidance, “Changes to an Approved Application: Biological Products.”

Rationale: The ability to make changes to the vaccine manufacturing process allows manufacturers to increase production output and reduce the overall cost of production. Vaccine manufacturers must be able to safely and efficiently incorporate



new technologies and scientific advances into their manufacturing process. FDA needs to provide technically sound and up-to-date guidance to industry regarding the reporting and filing expectations for manufacturing changes to an approved vaccine. Such guidance will increase regulatory predictability, and allow manufacturers to anticipate and accommodate for any Agency filing requirements.

DELIVERY PROPOSALS:

A. GAO Study and Report on the Impact of Medicare and Medicaid Reimbursement Levels on Access to Vaccines

Proposal: Propose a Government Accountability Organization (GAO) study on the impact of Medicare and Medicaid reimbursement levels on access to vaccines, especially for adults and the elderly, as well as all populations located in rural and underserved communities. The GAO should examine whether current levels of reimbursement or exclusion of vaccines from specific programs affects their use by physicians or access for beneficiaries.

Rationale: This report will help assess the amount to which reimbursement levels for providers and complex payment systems such as Medicare Part B and D impact access to vaccines for many Americans. A better understanding of the impact of these systems on access could lead to bipartisan solutions to several issues that may be barriers to adult immunization and immunization in underserved areas.

B. Affordable Access to Part D Vaccines

Proposal: Propose that the Centers for Medicare and Medicaid Services (CMS) encourage Medicare Part D plans to place preventive vaccines in the lowest co-pay tier to help increase access for beneficiaries.

Rationale: Ensure that Medicare beneficiaries have affordable access to vaccines recommended by ACIP.

C. Including the Cost of Programs to Increase Adult Immunization in Plans' Medical Loss Ratios

Proposal: Propose that private plans and Medicare Part D plans that institute programs to increase adult immunization be able to apply the cost of said programs to their medical loss ratio (MLR) as a cost of delivering medical care.

Rationale: To encourage private plans and Medicare Part D plans to institute programs to increase adult immunization.

D. Interoperability of EHRs & IIS



Proposal: Propose that Congress direct CMS to improve the use and interoperability of EHRs with IIS. To maximize the utility of IIS and EHR data systems, Congress should direct CMS and the Office of the National Coordinator (ONC) to evaluate and report on the current EHR standards to determine if they comprehensively capture the information needed to track the real-world use and implications of vaccine interventions across all ages, especially for adults with underlying chronic conditions or in underserved areas. Congress should direct CMS to engage in a process with vaccine and other interested stakeholders to refine interoperability standards further and improve their uptake—particularly among providers practicing in rural communities, working with vulnerable patient populations or vaccinating in community immunization sites, such as pharmacies, public health clinics and school-based clinics—and make the resulting, de-identified data available to interested stakeholders in a timely manner.

E. Greater Alignment Between CDC and CMS

Encourage greater alignment between CDC and CMS to ensure timely patient access to ACIP recommended vaccinations.

Proposal #1: Direct the CDC Director to publish new immunization recommendations within 120 days of an ACIP vote.

Proposal #2: Direct the Secretary to review and update relevant CMS coverage policies or other contractor guidance within 90 days of the publication of these CDC recommendations for alignment with vaccination recommendations applicable to Medicare beneficiaries.

F. CDC Review of Consistency within Vaccine Recommendation Process

Proposal: Propose that the CDC review the consistency with which the Advisory Committee on Immunization Practices (ACIP) approaches the evaluation and recommendation process for vaccines.

Rationale: This review could help improve the ACIP's deliberations process to ensure that the criteria for evaluation are aligned between vaccines and that all ACIP voting members and stakeholders are able to understand how the working groups have assessed the data in their decision-making process.



Delivery-Side Proposals

I. PROTECTING PATIENT ACCESS TO INNOVATIVE THERAPIES

A. Medicare-Specific Proposals

- **Appealability in Medicare Part D:** Just this year, the Senate Special Committee on Aging expressed concern with the inability of Medicare Part D beneficiaries to appeal for a lower-tier cost-sharing amount to be applied to a therapy placed on a plan's specialty tier.¹ Appealability is an especially important tool to improve patient access to needed therapies placed on a plan's specialty tier since cost-sharing for therapies can exceed 33 percent. While currently unavailable to Part D beneficiaries, this "appealability" of specialty-tier therapies often is available to patients in the commercial market and appealability, in general, is available to Part D beneficiaries for all drugs except those on the specialty tier.² Thus, Congress should include, as part of its 21st Century Cures legislation, the ability of Part D beneficiaries to appeal for a lower-tier cost-sharing amount to be applied to a specialty-tier therapy.
- **Enhance Safeguards for Medically Stable Patients Subject to Non-Medical Switching:** In Medicare Part D, the Centers for Medicare & Medicaid Services (CMS) currently prohibits plans from "implement[ing] prior authorization or step therapy requirements that are intended to steer beneficiaries to preferred alternatives" for patients stable on therapies included in the six protected classes.³ CMS applies this policy to beneficiaries already enrolled in a Part D plan as well as to new enrollees who were actively taking a therapy prior to enrollment in a plan. BIO believes such a policy is important because patients who are stable on a therapy should be able to remain on that therapy, as long as they and their provider feel it is necessary. This is important because individual patients are likely to respond differently to different therapies—even those within the same class—which can significantly impact their adherence to a therapy (e.g., if one therapy causes negative side-effects), and, in turn, their health outcomes. Thus, BIO recommends that the Committee consider extending this patient protection—to allow patients who are already stable on a therapy to remain on that therapy both within a plan year and when switching plans—beyond just the six protected classes to all Part D beneficiaries stable on a therapy. For example, to implement this policy, the "burden of proof" for switches could be revised to require Part D plans to demonstrate the clinical benefit of changing therapies, rather than the current standard, which requires clinicians to object and justify overriding a switch. Further, plans could be required to disclose to all enrollees the details of

¹ Senate Special Committee on Aging. March 10, 2014. Letter to Marilyn Tavenner (Available at: http://www.aging.senate.gov/imo/media/doc/03.10.14_CMS%20Part%20D%20Appeals%20Letter2.pdf).

² See Medicare Prescription Drug Benefit Manual. 2010 (Revision 10). 30.2.4 Specialty Tiers (Available at: <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/Chapter6.pdf>).

This Manual direction is based on 42 C.F.R. 423.578(a)(7).

³ CMS, Medicare Prescription Drug Manual, Ch. 6 § 30.2.5.

their therapeutic switching programs (TSPs), generally, and their clinical rationale for each switching event, in particular. Additional oversight and review of TSPs could be required of CMS to raise awareness regarding the financial incentives that plans have to switch patients and the non-clinical nature of most switching practices.

- **New Technology Add-On Payments (NTAP) in the Hospital Inpatient Prospective Payment System (IPPS)**: Congress should consider changes to the process of obtaining an NTAP under the IPPS. Such changes should take into account how the development of new technologies is incentivized through appropriate reimbursement in other care settings—such as the pass-through payment in the hospital outpatient prospective payment system—but also consider that additional incentives may be required to overcome the barriers to the use of new therapies in the inpatient space due to bundled payment reimbursement in that setting. These changes also should respond to concerns that the current process and criteria by which therapies are assessed is cumbersome, lengthy, and opaque, often leading to a delay in the use of new, innovative therapies in the hospital inpatient space. For example, Congress should consider redefining the newness criteria for an NTAP⁴ to refer to the date of approval for each indication rather than the date of the first approved indication. This is especially important for drugs and biologics targeting rare diseases to ensure that patients, for whom other treatments are often nonexistent, are able to access these therapies as soon as they reach the market and to ensure the preservation of incentives to develop therapies in this space. Additionally, Congress should consider the adequacy of current NTAP payment level: NTAP payment amounts⁵ may be insufficient for hospitals to cover the costs of the new technology. Raising the payment standard from 50 percent to 80 percent would be consistent with other mechanisms (such as outlier payments) in which there are shared risk for factors or costs extending beyond hospitals' direct control.
- **Improving Transparency in Medicare Coverage Determinations**: Congress should direct CMS to improve the Local Coverage Determination (LCD) process by adding requirements/ parameters to enhance openness and transparency and protect opportunities for stakeholders to provide feedback. The National Coverage Determination (NCD) process is established in statute and regulation, as opposed to the LCD process, which is entirely described in CMS' manuals. Though CMS could make changes to the current process without legislative direction, Congressional attention could help to focus the Agency's efforts on this issue. Important changes would include transparency in the process so that stakeholders both (1) know about proposed LCDs; and (2) have ample opportunity to work with clinicians and other scientific and technical experts to develop comments on those proposed LCDs.
- **Payment for Drugs and Biologics Prescribed in Hospital Outpatient Departments**: To encourage development of cutting-edge drugs and biologics, Congress should ensure that CMS pay separately for all drugs and biologics, including diagnostic radiopharmaceuticals, with Healthcare Common Procedure

⁴ 42 C.F.R. 412.87(b).

⁵ The NTAP amount is equal to the lesser of: (1) 50 percent of the amount by which the total covered costs of the case exceed the MS-DRG payment, or (2) 50 percent of the costs of the new technology. 42 C.F.R. 412.88(a)(2).

Coding System (HCPCS) codes that are administered in hospital outpatient departments and ambulatory surgery centers. These drugs and biologics should be paid separately at the statutory default of ASP plus six percent, just as they are in physician's offices, with the exception of vaccines which are subject to different payment rules. Congress also should prohibit CMS from reclassifying categories of drugs and biologicals (e.g., distinguishing between drugs and biologicals that serve a therapeutic modality and those used with other services) in order to circumvent statutory payment provisions. In addition, CMS should post all reported ASP rates on the drugs and biologics files. Any drugs approved under section 505 of the Federal Food Drug and Cosmetic Act (FFDCA) and all biologicals licensed under section 351 of the Public Health Service Act not only should be paid separately based on their ASP, but they also should continue to be eligible for drug and biological pass-through status in order to encourage development of cutting edge drugs and biologics for 21st Century Cures.

- **Accurate Reporting of the Prescription of Drugs and Biologicals in Hospital Outpatient Departments:** Congress should require CMS to maintain unique HCPCS codes for all drugs, biologics, and diagnostic radiopharmaceuticals to ensure accurate reimbursement rates and to facilitate data analysis. Additionally, to the extent that Medicare reimbursement for some drugs and biologicals continues to be packaged under the Hospital Outpatient Prospective Payment System, CMS guidelines must go beyond simply encouraging hospitals "to change their reporting practices if they are not already reporting HCPCS codes for all drugs and biologicals furnished, when specific HCPCS codes are available for those drugs and biologicals."⁶ A clear requirement from CMS that hospitals must bill Medicare for drugs and biologicals using both HCPCS codes and revenue code 636 is critical to ensuring that CMS has the data necessary to facilitate appropriate rate-setting in the future. This requirement also would help CMS to satisfy the requirement established in the Affordable Care Act (ACA) to measure drug utilization to calculate the pharmaceutical tax.

B. Non-Medicare-Specific Proposals

Incentivizing Innovation in Alternative Payment Models (APMs): CMS increasingly is working on alternative payment models (APMs) to achieve the "triple aim" of higher quality care for individuals, better health for populations, and lower per capita costs. BIO believes that alternative payment methodologies and delivery of care models have great potential to achieve these aims and can be structured to adapt to new emerging technologies and cures while still incentivizing the development of cures. However, we also have concerns that improperly designed APMs risk incentivizing the underutilization of care and, if they mainly focus on cost-containment, can limit patient access to innovative therapies. In fact, the reimbursement structure of APMs not only has a direct impact on patients' short-term access to innovation, but can establish trends that, in the longer-term, disincentivize cutting-edge research and development and stunt the progress of future innovation. To ensure that APMs are fostering an environment that supports the development of modern treatments and cures, while providing quality patient care today, Congress should require all payment demonstration projects—including those conducted by the Center for Medicare and Medicaid Innovation—to specify how they will protect access to innovative therapies.

⁶ 77 Fed. Reg. at 68,389.

Specifically, CMS should be required to include mechanisms within APMs that account for the emergence of new technologies and the evolution of medicine and science. This is especially important since these models often are built using retrospective data that inherently may not reflect increasingly personalized medicine, potentially disadvantaging beneficiaries whose providers participate in APMs. One way to account for new technologies is to incorporate a temporary pass-through payment mechanism, similar to what exists for new technologies in the hospital outpatient space. This pass-through payment would reimburse providers separately for the use of these technologies, which may offer significant patient benefit, but would have not been accounted for in a bundled payment system that is built from a retrospective analysis of the costs of providing care to a specific patient population. This pass-through payment also should be exempted from inclusion in the financial measures that affect provider reimbursement, to ensure that providers can utilize the new technologies without being financially penalized until the value of these therapies can be assessed (likely at least 2 years).

An additional protection CMS should consider for providers at financial risk through participation in an APM is an outlier payment that recognizes the inherently higher costs associated with providing quality care to certain patients (e.g., those with complex or chronic conditions, potentially with several comorbidities or other underlying health issues). This type of outlier payment—which exists for Medicare beneficiaries in the hospital inpatient space—would better ensure that providers are not penalized for treating high-cost patients, and, in turn, that these patients would be able to access necessary care.

In keeping with a focus on improving quality of care, not just decreasing the overall costs of care, the Committee should direct CMS to establish a mechanism to reimburse for services that improve care coordination and otherwise improve patient support in APMs. One way CMS could accomplish this is to provide an additional reimbursement amount for care coordination services for which HCPCS codes were created and valued by CMS (e.g., Current Procedural Terminology codes 99495 and 99496 or the chronic care management services proposed for valuation in the Calendar Year 2015 Medicare Physician Fee Schedule).

Finally, to leverage this spectrum of care, CMS should work with stakeholders to consider how best to incentivize coordinated patient care within APMs that does not disadvantage the assessment of care provided by one type of provider in comparison to another. In general, existing APMs tend to focus on the unique needs of the primary care provider and the immediate primary care needs of the patient. However, this limited focus—on one point of care in a patient’s interaction with the healthcare system and on near-term care needs—risks missing an opportunity to streamline the coordination and efficiency of care provided to a patient by a spectrum of healthcare professionals.

Implementing the Statutory Nondiscrimination Provisions Included in the ACA: The ACA included nondiscrimination provisions prohibiting plans from discriminating against patients based on demographics and underlying health status.⁷ However, the Center for Consumer Information and Insurance Oversight (CCIIO)—responsible for overseeing the federally-facilitated Exchanges—does not robustly review plans’ benefit designs for compliance with such nondiscrimination requirements, despite the fact that formulary structure and the scope of provider networks can be mechanisms for discriminating against patients with specific conditions (e.g., placing all therapies to treat specific types of conditions on a specialty tier, which effectively excludes patients with these conditions

⁷ ACA § 1302(b)(4); and, ACA § 1311(c)(1)(A).

from enrolling in a plan). Indeed, specialty tier formulary designs and narrow provider networks have become particularly prevalent on the Exchanges,⁸ even though they may discriminate against patients with certain medical conditions by imposing substantial cost-sharing obligations on the categories of benefits or types of therapies on which they rely or restricting access to the specialty providers most appropriate to treat their condition(s), respectively. As just one example, due to the potential lack of expertise about rare diseases in some provider networks, some patients with rare diseases have to seek care from specialists, who may even be located in a different state. As a result, some patients can be subject to higher out-of-pocket costs and no minimum limits.

Congress should direct CCIIO to enforce the nondiscrimination requirements already in statute to ensure plans with discriminatory benefit designs and overly narrow provider networks are not offered in the marketplace. One way to accomplish this is to require CCIIO to certify, at least on an annual basis, that qualified health plans (QHPs) meet existing nondiscrimination requirements. Additionally, Congress could give CCIIO express statutory authority to impose sanctions on QHPs that fail to meet the ACA's non-discrimination requirements. CCIIO also should be encouraged to work closely with states to ensure all QHPs are held to the same standards of nondiscrimination.

II. SUSTAINING INCENTIVES FOR INNOVATION

- **Modifications to Promote Value-Based Contract Arrangements:** Value-based contracting is gaining traction in non-U.S. markets and is a concept that could be adapted domestically to promote patient access to new discoveries and cures. The industry, in general, is open to potentially pursuing innovative, value-based approaches, as long as they do not negatively affect patient access to innovative products more broadly. However, certain hurdles exist to the widespread utilization of these programs. For example, laws designed to protect against fraud and abuse in “traditional” healthcare delivery and payment systems, such as the Federal Anti-kickback Statute (AKS), may dissuade manufacturers from offering certain innovative contracting arrangements. Another hurdle to value-based contracting is the application of existing laws and regulations for Medicare Average Sales Price (ASP), Medicaid best price, Average Manufacturer Price (including “5i” AMP), prices offered under the Veterans Health Care Act (including Annual Non-Federal Average Manufacturers Price, Federal Supply Schedule/Federal Ceiling Price, and the TRICARE Retail Pharmacy Refund program), and other government pricing calculations, which can result in uncertain and potentially disproportionate negative impacts for certain types of contracting strategies.

In order to facilitate the use of value-based contracting in the U.S., the Committee should create legislative carve-outs for Best Price and all other government pricing calculations and requirements as they relate to products sold or transferred under value-based contracts. To allow for the flexibility needed in the evolving value-based contracting space, Congress should require CMS to work with stakeholders—including industry, providers, patient and caregiver representatives, and payers—to establish parameters through notice-and-comment rulemaking for contracts that meet this statutory exemption (e.g., value-based contracts that financially incentivize

⁸ See Avalere Health. 2014. Consumers Likely Face High Out-Of-Pocket Costs for Specialty Drugs In Exchange Plans (Available at: <http://avalere.com/expertise/managed-care/insights/consumers-likely-face-high-out-of-pocket-costs-for-specialty-drugs-in-excha>). See also McKinsey&Company. 2014. Hospital networks: Updated national view of configurations on the exchanges (Available at: <http://healthcare.mckinsey.com/hospital-networks-updated-national-view-configurations-exchanges>).

measurable quality of care or positive health outcomes). Congress should require CMS to finalize these regulations within one year of the enactment of the statutory carve-outs. Additionally, Congress should expand existing, or create new, statutory exceptions to the AKS to clearly protect innovative value-based contract arrangements that meet certain requirements (e.g., that promote patient access and pose a low risk of patient or program abuse), and direct the Health and Human Services Office of Inspector General to implement such exceptions through the creation of new regulatory safe harbors.

III. **BUILDING AN EFFICIENT, LEARNING HEALTHCARE SYSTEM**

- **Coding**: Congress should require CMS to issue J-codes quarterly, as is current policy for granting pass-through status and issuing temporary codes. This change is needed to respond to the lag-times—which can be as long as 21 months between when a therapy is available on the market and when it receives a permanent J-code—created by the existing process of issuing codes only once a year. For example, a new drug or biologic approved by the FDA on April 1, 2014 will not receive a J-code until January 1, 2016. Such delays result in logistical complexities and confusion at the point of care that can delay patient access to innovative new drugs and biologicals. In tandem with this requirement, Congress should require that CMS report on the technological and logistical (and any other) barriers to issuing J-codes and mechanisms for addressing these barriers within one year of the effective date of the legislation, in order to move toward a goal of issuing J-codes quarterly.
- **Timely Access to Data**: Except where data are proprietary or commercially sensitive, Congress should make available data generated or governed by federal resources (e.g., Medicare data, including Part D data; data from plans offered through the ACA-created health insurance Exchanges; Medicaid data, including managed care data; quality metrics data, for example, data collected by the Medicare Physician Quality Reporting System) and remove any existing barriers that hinder access to these data by all stakeholders, not just researchers. Further, CMS could be required to finalize claims data—such as those data made available to stakeholders as part of the annual fee schedule notice-and-comment rulemaking processes—within one year, as opposed to the current two year lag, to better track the impact of changes in federal policy in a timely manner.
- **Facilitating Patients' Awareness of Assistance Programs**: Congress should reexamine the Health Insurance Portability and Accountability Act (HIPAA) limitations on the transfer of information from covered entities to non-covered entities, to permit the transfer of information to non-covered entities for the purpose making patients aware of available patient assistance programs (PAPs).^[1] Access to patient assistance programs is important for many patients to ensure they are able to obtain the therapies prescribed for them without incurring excessive costs and to receive support during the course of their treatment. Current requirements permit covered entities to share information for treatment, payment or health care operations only to other covered entities or business associates of the covered entity, with limited exceptions. This proposal responds to existing concerns that requiring covered entities, and their business associates, to obtain patient authorization prior to

^[1] See 45 CFR 164.506(c)(3)...a covered entity may disclose protected health information to another covered entity or a health care provider for the payment activities of the entity that receives the information.

providing information to non-covered entities administering PAPs unduly delays the process of helping patients get access to needed therapies. To address this issue, Congress should consider excepting from HIPAA the transfer of limited PHI between covered entities and non-covered entities administering PAPs, for the limited purpose of making patients aware of these programs. Additionally, Congress should direct HHS, in consultation with stakeholders, to identify criteria that an organization administering a PAP must meet to be considered eligible for this exception.

- **Improving the Utility of Electronic Health Records (EHRs) to Track Real-World Implications of Therapeutic Interventions:** The growth of the information captured in, and the number of providers utilizing, EHRs has created a unique opportunity to better characterize outcomes associated with a specific medical intervention or therapy in a given patient population. In the context of drugs and biologics specifically, EHRs present significant promise in linking specific clinical outcomes, including adverse events, to a specific product, lot number, and manufacturer. Data collected from EHRs also may be useful in research intended to advance the knowledge and quality of interventions. For example, the information could be used in post-market studies of interventions already available to patients. To maximize the utility of EHRs, Congress should direct CMS to evaluate and report on the current EHR standards to determine if they comprehensively capture the information needed to track the real-world implications of therapeutic interventions (i.e., accurate and specific information regarding a drug and its manufacturer). CMS also should engage stakeholders to refine these standards further, improve their uptake—especially among providers practicing in rural communities or working with vulnerable patient populations—and make the resulting, de-identified data available to interested stakeholders in a timely manner.
- **Representation of Innovators Within the Medicare Payment Advisory Commission's (MedPAC's) Membership:** BIO believes that MedPAC should adequately ensure it takes into account the important role of biopharmaceutical innovation in making its recommendations to Congress. Specifically, MedPAC's membership requirements should be aligned such that its membership reflects the expertise and perspective of the innovative biopharmaceutical industry. For example, the Patient-Centered Outcomes Research Institute (PCORI) reflects such expertise by requiring the inclusion of "3 members representing pharmaceutical, device, and diagnostic manufacturers or developers."
- **Clarity in Provider Incentive Programs:** Improving patient decision making at the point of care is an increasingly important goal as scientific and technological advances allow our healthcare system to progress toward truly personalized medicine. To add to ongoing efforts to better inform patients, Congress should direct the Secretary to establish a mechanism for insurers to report, and patients to be able to obtain, information on whether providers are receiving financial incentives to adhere to particular delivery of care regimens and what form those incentives take. This mechanism must include the timely update of information in a format easily accessible and understandable by the average healthcare consumer, and HHS should consult with interested stakeholders in its design and implementation. We believe that this proposal would contribute to empowering patients with information to work with their providers to make the best treatment decisions for them.
- **Integrating Data on Health Outcomes and Costs Across Medicare and Medicaid Programs:** Care provided to beneficiaries in one arena of the healthcare system (e.g., prescription drugs prescribed by a physician) can have an impact on

outcomes and costs accrued in other arenas (e.g., need for hospitalization, surgical interventions, emergency department visits). However, in the current system, this impact is not captured, in part, because of the siloed nature of the different Parts of Medicare. This reality is increasingly at odds with CMS's focus on better integrating patient care, for example, through the Value-Based Payment Modifier program, and demonstration projects involving medical homes, Accountable Care Organizations, and those targeting integrated care for Medicaid beneficiaries (e.g., the ongoing Medicare/Medicaid dual eligible demonstration). As one step towards better reflecting that care provided in one healthcare setting can impact the health outcomes and costs in other settings, we propose that Congress direct CMS to work with stakeholders to design and implement a pilot program that identifies and assigns cost-savings (e.g., in the form of decreased hospitalizations) resulting from the use of prescription drugs and biologicals. Though these savings potentially accrue to Medicare Parts A and B, the pilot program would work to reflect such savings in a way that is meaningful to Medicare Part D plan sponsors (e.g., incorporate such savings as a component of a plan's star rating). We recognize that the feasibility of such an assessment will hinge, in part, on the ability to construct an attribution methodology to assign patients' incurred costs and health outcomes to specific providers in manner that is consistent with the level of influence a provider may have had. Nonetheless, the success of such a model would not only better reflect the value of these therapies to the healthcare system overall, but it could reinforce the need to ensure patients' access to innovative therapies and cures.

- **Protections Needed for Any Policies Utilizing Alternative Delivery of Care or Payment Models, including Any Use of Clinical Pathways:** Congress should consider policies to ensure that any use of clinical pathways by Medicare and Medicaid—whether in the fee-for-service arena or in managed care arrangements—does not come at the expense of high-quality patient care and that these programs can continue to adapt to changes in medicine and treatment options. Specific considerations the Committee should take into account in drafting legislation include:
 - Promoting patient and provider choice and adaptability to innovation, consistent with the approach taken in Medicare's use of compendia in Medicare Part B;
 - Requiring an open process for all proposed reforms to current delivery of care or payment models, including input from patients, providers, and other stakeholders into their development and content;
 - Ensuring that changes to delivery of care models used in public programs allow patients and providers to choose from the range of available treatment options and support the tailoring of care to individual patient needs, in accordance with diagnostic information, clinical practice guidelines, compendia, and principles of evidence-based medicine;
 - Ensuring that all information and methodologies founding alternative delivery of care or payment models used in public programs are made publicly available and include a description of the evidence and information sources used;
 - Ensuring that patients are made aware that their provider is being incentivized to provide care (e.g., according to a clinical pathway); and,
 - Ensuring that financial incentives to prescribers that are impermissible for the biopharmaceutical industry are not allowed for payers, either.