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Getting by with a Little Help from Their Friends: FDA Using External Experts to Enhance Biomarker Qualification and Enable Precision Medicine

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ABSTRACT:

Biomarkers are essential tools in expediting the development of new drugs, particularly Precision Medicines. While an innovator biopharmaceutical company often utilizes biomarkers to support developing their own drug, innovators may also seek to have biomarkers "qualified" by FDA. "Qualification" is an FDA determination that within an approved, specific context of use (COU) the qualified biomarker can be relied upon to have a specific use or interpretation to support drug development. That is, the biomarker will be publicly available for its COU to support any innovator's applicable drug development program and application, without the need for FDA reviewers or the innovator to reconfirm the validity of the biomarker for its COU. Recognizing the need to help accelerate biomarker qualification, Congress, in passing the recent 21st Century Cures Act, effectively statutorily codified FDA's biomarker qualification process and included provisions for FDA to utilize external experts at the agency's discretion. This paper argues the agency should follow historical precedent, fully utilizing an external expert consortium to conduct first substantive reviews and to make recommendations to FDA on biomarker submissions. We recommend the agency pilot this approach to explore further considerations such as application of its conflict of interest rules, process timelines, and costs involved.

INTRODUCTION

Precision Medicines,[1] designed to be "a more quantitative, mechanism-based understanding and prediction of health, disease, and response to interventions,"[2] offer the potential for better outcomes for patients than traditionally-developed medicines.

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[1] While this paper generally speaks from the perspective of biomarkers accelerating drug development, clearly FDA-qualified biomarkers benefit development of drugs, biologics, medical devices, Lab Developed Tests (LDTs), etc., as well as the practice of medicine and delivery of healthcare.

[2] J. Woodcock, *"Precision" Drug Development?*, 99.2 CLINICAL PHARMACOLOGY & THERAPEUTICS 152, 152 (2016).

Biomarkers are distinct biochemical or physiological measures of the state of a disease or the characteristics of patients. Many biomarkers are used to help develop new therapeutic products[3] or to understand existing treatments. They can measure, for instance, whether patients are responding to a therapeutic. Even better, biomarkers can help to predict which subpopulations of patients will respond favorably to a given drug. In some cases, "using appropriate biomarkers can make it possible to dramatically decrease the sample size required to achieve statistical significance—for example, from 1500 to 50 patients,"[4] thereby lowering the necessary human experimentation and costs of drug development. While innovators routinely use biomarkers to help develop their own therapeutics, sometimes innovators may seek to have a biomarker "qualified" by the Food and Drug Administration (FDA) for generalizable use. That is, they may seek to have FDA approve a specific context of use for a given biomarker so that the biomarker may be used by anyone without having to re-substantiate the biomarker's suitability for its FDA-approved use. Qualified biomarkers can accelerate new therapeutic development by providing transparent, FDA-recognized criteria for all innovators to target or to include in their development programs. The development of next generation cures and precision medicines could depend, to an important degree, on FDA's qualification of biomarkers.

Although FDA has offered a means to qualify biomarkers for more than a decade, as of December 2016 there were only six instances of qualified biomarkers.[5] One barrier to producing qualified biomarkers is the finite R&D resources available to research and qualify them. Also, in many cases, there is simply inadequate knowledge or consensus on the biochemical, genetic, or pathophysiological pathways within a disease. There is also a need for FDA to articulate the evidentiary requirements for biomarker qualification and a need for greater agency capacity and capability to operate its biomarker qualification process. While the agency has made progress on developing an evidentiary framework for qualifying biomarkers,[6] FDA should also improve its biomarker qualification process capacity and capability by using external experts to review submissions and make recommendations to the agency. This would align with FDA's tradition of using external experts to make recommendations to the

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[3] While this paper generally speaks from the perspective of biomarkers accelerating drug development, clearly FDA-qualified biomarkers benefit development of drugs, biologics, medical devices, Lab Developed Tests (LDTs), etc.

[4] PRESIDENT'S COUNCIL OF ADVISORS ON SCI. AND TECH., EXEC. OFFICE OF THE PRESIDENT, PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION, 21, n.62 (2012), https://www.broadinstitute.org/files/sections/about/PCAST/2012%20pcast-fda.pdf (last visited Sept. 15, 2017) ("The drug imtainib (Gleevec) was approved based on a clinical trial of only fifty-four patients, because nearly all patients showed marked benefit [http://www.cancer.gov/newscenter/qa/2001/gleevecqa]. The drug gefitinib (Iressa) required a clinical trial of approximately 1500 patients because it showed benefit in only a minority of patients. It later became clear that testing the drug in the specific subset of patients carrying mutations in a specific gene (EGFR) would have made it possible to demonstrate efficacy in only about a hundred patients.").

[5] *See* FOOD & DRUG ADMIN., LIST OF QUALIFIED BIOMARKERS, (Nov. 16, 2016), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm (last visited Oct. 10, 2017).

[6] FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH, FRAMEWORK FOR DEFINING EVIDENTIARY CRITERIA FOR BIOMARKER QUALIFICATION, (October 20, 2016), https://fnih.org/sites/default/files/final/pdf/Evidentiary%20Criteria%20Framework%20Final%20Version%20Oct%2020%202016.pdf [https://perma.cc/6RNZ-NGGL].

agency and fully implement the relevant provisions in the recently enacted 21st Century Cures Act.[7]

In Part I of this paper, we define key biomarker terms and review basic types of biomarkers used to accelerate therapeutic product development. We discuss biomarker qualification and its importance to helping all therapeutic product innovators. We then review FDA's current biomarker qualification process. We also describe FDA's existing, three-stage qualification process.

In Part II of this paper, we review FDA's considerable history of using external experts, as directed by both Congress and the Executive. We review FDA's administrative authorities for using external expertise, including reviewing recent agency use of that authority. We then discuss agency management of experts' potential conflicts of interests.

In Part III, we recommend inserting panels of external experts, convened from a suitable partner organization, at the second (Consultation and Advice) and third (Review) stages of the qualification process. The paper concludes by discussing further considerations for implementing an external expert supported FDA biomarker qualification process.

I. BIOMARKERS IN DRUG DEVELOPMENT

A biomarker is a characteristic that measures as an indication of "normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention."[8] One example is measuring a patient's blood cholesterol levels to help identify a risk of developing heart disease; or, after a diagnosis of heart disease, to help make ongoing treatment decisions about what, if any, intervention or drug dose may be effective for the given patient. FDA and NIH sponsored a working group to help harmonize biomarker terminology and categorize biomarkers based on the role a given biomarker can play in drug development and research.[9] Biomarker categories commonly relied upon in drug research and development include:

- Predictive Biomarkers – A biomarker used to identify individuals who are more likely than similar patients without the biomarker to experience a favorable or unfavorable effect from a specific drug or intervention. Predictive biomarkers are specific for an individual drug and are not generalizable for all drugs treating a given disease, yet they play an important role in the utility of the specific drug to which they are applicable. For example: Although many therapeutics may be available to treat Non-Small Cell Lung Cancer (NSCLC), utilizing predictive biomarkers can help to optimize therapeutic agent selection. A patient with Epidermal Growth Factor Receptor (EGFR) mutations in their NSCLC may have a better outcome with a drug having established efficacy in patients where that mutation is present. In this example, the EGFR mutation serves as the predictive biomarker to

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[7] 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

[8] Ctr. for Drug Evaluation and Research, Food & Drug Admin., Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools, at 3 (2014), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf (last visited Sept. 15, 2017).

[9] FDA-NIH BIOMARKER WORKING GRP., FOOD & DRUG ADMIN., BEST (BIOMARKERS, ENDPOINTS, AND OTHER TOOLS) RESOURCE, (2016), https://www.ncbi.nlm.nih.gov/books/NBK326791/pdf/Bookshelf_NBK326791.pdf [https://perma.cc/2U63-D79E].

enable healthcare professionals to select a "Precision Medicine" treatment approach for that patient.[10]

- Prognostic Biomarkers – In an individual with a disease or medical condition, prognostic biomarkers help identify the likelihood of a clinical event, disease recurrence, or progression of disease. Identifying such patients can provide indicators of the rate of progression or state of the disease in patients. As an example: BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as a prognostic biomarker to help identify women who may have a greater or lesser likelihood of a second breast cancer. Since they measure the progress or state of the disease, prognostic biomarkers help ensure clinical trials contain patients more likely to have the same stage or state of a targeted disease to more efficiently and effectively measure a drug's effect in a more homogenous patient population.
- Pharmacodynamic/Response Biomarkers – A biomarker that can be used to show a biological response has occurred in an individual who has received a drug or an intervention. Measuring this response can be important for new diseases or new drugs, particularly those that are the first therapies developed for a given disease. As a well-known example: Blood pressure may be used to assess the response in hypertensive patients taking antihypertensive agents. Sometimes drug action measured by a pharmacodynamic/response biomarker may represent activity against the underlying disease state and, as such, some Pharmacodynamic biomarkers could eventually become Surrogate Endpoints (see below). In fact, blood pressure is also an FDA-recognized surrogate, in particular contexts of use, for myocardial infraction, heart failure, and stroke.[11]
- Safety Biomarkers – A biomarker used to indicate the presence or extent of toxicity related to a drug or an intervention. These biomarkers can measure drug safety parameters in both clinical and preclinical testing, helping to establish uniformity and comparability for drug safety testing. As an example: Certain animal urinary biomarker panels (e.g., Kim-1, Albumin, Total Protein, et al.) are used to detect forms of drug-induced kidney damage during preclinical toxicological testing.[12]
- Surrogate Endpoints – An endpoint, which can include biomarkers, that is a substitute for a direct measure of how patients feel, function, or survive, independent of the particular drug or intervention acting on the surrogate.[13] Therapeutic product effect on the surrogate endpoint effectively becomes a basis for regulatory approval. Biomarkers which are surrogates are considered rare, but are highly valuable for accelerating drug discovery as they enable determination of drug efficacy earlier and/or with fewer patients than would be required by using traditional disease endpoints (e.g., how the patient feels, functions, or survives). One example of a surrogate endpoint:

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[10] *See, e.g.*, Megan Baumgart & Kishan Panya, *The Use of Biomarkers in the Treatment of Non-Small Cell Lung Cancer*, 1.1 EXPERT REV. OF PRECISION MED. AND DRUG DEV., 25, 31 (2016).

[11] *See* FOOD & DRUG ADMIN., *FDA Biomarkers: Facts and Surrogate Endpoints*, https://www.fda.gov/aboutfda/innovation/ucm512503.htm) [https://perma.cc/6KLN-M4G2].

[12] *See, e.g.,* Conall M. O'Seaghdha, et al., *Analysis of a Urinary Biomarker Panel for Incident Kidney Disease and Clinical Outcomes*, 24.11 J. AM. SOC'Y OF NEPHROLOGY, 1880, 1884–5 (2013).

[13] FDA-NIH BIOMARKER WORKING GRP., *supra* note 9, at 39–49.

> HIV-RNA blood level reduction is a validated surrogate endpoint for human immunodeficiency virus (HIV) treatment and has been used for the basis of Accelerated Approval for some drugs intended to treat HIV.[14]

The above categories help demonstrate the wide-ranging, complex utility of biomarkers in supporting new therapeutic product research and development. A given biomarker sometimes can be utilized in more than one way, making it fall into more than one of the above categories. As a simple example: monitoring a patient's "blood cholesterol/lipid levels" could serve, even simultaneously, to help estimate the likelihood of that patient experiencing a clinical event like a heart attack (i.e., as a Prognostic Biomarker), as well as potentially indicating whether the patient is responding to an intervention; evidenced, hypothetically, by a lowering of the marker to normal levels (i.e., as a Pharmacodynamic/Response biomarker). Hence, biomarkers supporting drug research and development are more specifically described and classified according to their Context of Use (COU): A statement that fully and clearly describes the way a given biomarker is to be used and the medical product development-related purpose of that use.[15] In the simple hypothetical above, one could imagine both a "Prognostic" and a "Pharmacodynamic" COU for the single biomarker "blood cholesterol and lipid levels."

Biomarker Qualification

While an innovator biopharmaceutical company often utilizes biomarkers within a proprietary setting to support researching and developing their own new drug—particularly Predictive Biomarkers—innovators may also seek to have biomarkers "Qualified" by FDA. "Qualification" is an FDA determination, based on a statutory process, that within the specified COU, the qualified biomarker can be relied upon to have a specific interpretation and application in medical product development and regulatory review.[16] Essentially, as long as FDA considers the biomarker qualified, any innovator may rely upon the biomarker for its approved COU in any product application without the need for FDA reviewers to reconsider, or for the sponsor to reconfirm, the suitability of the qualified biomarker. In this sense, a qualified biomarker's COU is somewhat analogous to an approved indication for a drug; communicating the purpose and context for which FDA has determined the biomarker may be used safely and effectively to support clinical development programs.

Qualified biomarkers help improve the efficiency and effectiveness of new therapeutic product R&D for all innovators by helping to reduce uncertainty.[17] Some R&D uncertainties are intrinsic to the science of drug research and development; for instance, the effectiveness of a drug may become better understood as it is tested in progressively larger clinical trial phases. In fact, clinical trial costs constitute the single largest component of the biopharmaceutical industry's R&D budgets.[18] A significant

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[14] *See* CTR. FOR DRUG EVALUATION AND RESEARCH, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND STAFF: HUMAN IMMUNODEFICIENCY VIRUS-1 INFECTION: DEVELOPING ANTIRETROVIRAL DRUGS FOR TREATMENT 4 (2015), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm355128.pdf (last visited Sept. 15, 2017).

[15] FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH, s*upra* note 6, at 3.

[16] FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH, *supra* note 6, at 8.

[17] *See, e.g.*, PRESIDENT'S COUNCIL OF ADVISORS ON SCI. AND TECH., *supra* note 4, at 12–13.

[18] *See, e.g.,* AVIK S. A. ROY, MANHATTAN INST. FOR POLICY AND RESEARCH, STIFLING NEW CURES: THE TRUE COST OF LENGTHY CLINICAL DRUG TRIALS 2 (2012).

portion of clinical trials' expenses can be attributed to the large patient population size and long timelines normally required to ensure a sufficient number of patients are enrolled who will have experienced or reached particular clinical events, disease states, or endpoints so that the drug's safety and efficacy can be evaluated for potential approval. Biomarkers qualified as Surrogate Endpoints clearly would reduce the time and costs for clinical trials since they allow approval of a drug based on an endpoint (i.e. the surrogate) reached more rapidly than traditional clinical endpoints. However, qualified biomarkers of all categories can help reduce the duration and costs of clinical development, and thus accelerate patient access to new therapeutics. For instance, qualified Prognostic Biomarkers can help identify specific subsets of patients at the same or similar state in the targeted disease, who hypothetically are more likely to experience particular clinical events or endpoints than a more random population of patients. Enrolling patients based on prognostic biomarkers can help establish a drug's safety or efficacy for initial approval with smaller clinical trials of more homogeneous patients, helping to speed patient and prescriber access to future medicines sooner.

Innovators also face regulatory uncertainties, such as understanding the type and quality of evidence that will be necessary to demonstrate initial safety or efficacy for FDA approval. Often this is determined through sponsor meetings and communications with the agency. However, the COU statements for qualified biomarkers help provide regulatory clarity to all innovators simultaneously without the need for each sponsor to have individual meetings with the agency to discuss similar therapeutic targets or requirements. Indeed, qualified Safety, Pharmacodynamic/Response, and Prognostic Biomarkers can communicate FDA expectations and help standardize the criteria to all innovators as to what responses or data will help demonstrate in which patients, and to what extent candidate drugs are safe and effective for approval. For example, FDA currently recognizes the reduction in glycated hemoglobin (Hb1AC) as one measure of efficacy or pharmacodynamic response for drugs developed to treat diabetes.[19] This recognition establishes a physiological target enabling innovators to plan and conduct their diabetes clinical programs with greater understanding of FDA's expectations. Having qualified biomarkers may help to explain FDA drug development expectations and requirements particularly for small, start-up innovators who may not be able to spread the costs of traditional drug development uncertainty across multiple development programs.

In addition to mitigating clinical and regulatory uncertainty, qualified biomarkers implement some of the highest principles of medical and research ethics: Since each innovator does not need to establish or reconfirm a qualified biomarker's COU for their applicable development programs, redundant or futile, human and animal testing can be avoided or reduced. The qualification process also encourages knowledge pooling and transparent data sharing between industry, academia, and patient organizations. Collaborations or consortia in support of biomarker qualification often represent state-of-the art knowledge from world-renowned subject matter experts and current patients regarding the pathophysiology, genetic nature, and patient experiences, even for as-yet untreatable diseases. The qualified COU's emerging from the collaborative ecosystem of FDA biomarker qualification would help articulate the

[19] CTR. FOR DRUG EVALUATION AND RESEARCH, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: DIABETES MELLITUS: DEVELOPING DRUGS AND THERAPEUTIC BIOLOGICS FOR TREATMENT AND PREVENTION 12 (2008), https://www.fda.gov/downloads/Drugs/ . . . /Guidances/ ucm071624.pdf (last visited Sept. 15, 2017).

scientific community's evolving understanding of a given disease or its patient population, and would have direct regulatory significance to help innovators develop new cures more efficiently. Further, accumulating knowledge can modify COU's, providing ongoing, transparent data to all innovators.

As a measure of the value of qualified biomarkers in reducing therapeutic product development uncertainty it is important to understand that biomarker qualification is a non-proprietary process. That is, there is no exclusivity, no immediate market access, and no intellectual property right attained by an innovator for qualifying any biomarker. In fact, the publication of data and the underlying hypothesis of a biomarker can potentially interfere with the pursuit of any related intellectual property rights. In addition, any therapeutic product using a qualified biomarker for its research and development must still independently demonstrate its safety and efficacy, and must still be approved by FDA, under the same rigorous "gold standard" as any other new therapeutic. Innovators have long-recognized the importance of scientific collaborations in researching drugs for complicated modern diseases such as cancers, Alzheimer's disease, ALS, etc. Although some other incentives could precipitate even more investment in biomarker qualification, the totality of the existing factors (e.g., reducing uncertainty, medical ethics, collaborations with patients and researchers, etc.) has already attracted many innovative biopharmaceutical companies into numerous consortia with patients, academics, and other stakeholders to seek qualification of a wide range of biomarkers for many diseases.

FDA Biomarker Qualification Process

FDA has evolved its biomarker qualification process over the past decade, which substantively informed the qualification process statutorily codified in the recently enacted 21st Century Cures Act.[20] In 2004, FDA called for "critical path research . . . to develop new, publicly available scientific and technical tools—including . . . biomarkers . . . — that make the [drug] development process itself more efficient and effective and more likely to result in safe products that benefit patients,"[21] specifically identifying the need for new biomarkers and surrogate endpoints. In 2007, noting the limited number of surrogate endpoints and biomarkers available to support therapeutic product development, and the absence of an agreed-upon, systematic, transparent process for biomarker evaluation, FDA requested the Institute of Medicine (IOM)[22] generate recommendations on a qualification process for biomarkers.[23] In 2010, FDA issued a draft guidance document describing a qualification process for Drug Development Tools, which includes biomarkers, and finalized this guidance in 2014.[24] However, as of August 30, 2017, FDA has not yet revised this 2014 final guidance to align fully with the qualification process articulated in the 21st Century Cures Act.

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[20] *Supra*, note 7.

[21] FOOD & DRUG ADMIN., INNOVATION OR STAGNATION: CHALLENGES AND OPPORTUNITIES REPORT 8 (2004), https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf (last visited Sept. 15, 2017).

[22] On April 28, 2015, IOM became the National Academy of Medicine (NAM).

[23] INST. OF MED. OF THE NAT'L ACAD. OF SCI., EVALUATION OF BIOMARKERS AND SURROGATE ENDPOINTS IN CHRONIC DISEASE, at 19 (Christine M. Micheel & John R. Ball eds., The National Academies Press, 2010).

[24] CTR. FOR DRUG EVALUATION AND RESEARCH, *supra* note 8.

The biomarker qualification process outlined in the 21st Century Cures Act contains three deliverables sequentially submitted for potential acceptance by the agency from the party seeking to qualify a biomarker (the "requestor"): A Letter of Intent (LOI), the Qualification Plan (QP), and the Final Qualification Package (FQP).[25] FDA's finalized 2014 guidance document describes a very similar three-stage process, including substantively the same LOI and FQP submitted at the first and third stages, respectfully.[26] However, the guidance's second-stage submission, "Initial Briefing Package," is replaced in the statutory qualification process with a "Qualification Plan" (QP). The statute does not specify required content for qualification process submissions, however the 2014 guidance describes the LOI "should include a short description of the [biomarker], its proposed COU, and a rationale to support qualification,"[27] and the FQP should contain complete and detailed descriptions of the studies and analyses which justify qualification of the biomarker for the intended COU.[28] While the statute requires the agency to issue guidance further describing the statutory qualification process,[29] the specific statutory designation of a "qualification plan" may imply congressional intent for a requestor obtaining good faith, a priori concurrence with the agency on specific evidentiary gaps and the data necessary to satisfy them in order to qualify the proposed biomarker. If so, the QP would help reduce the uncertainty in investing in qualification efforts and potentially attract more biomarker submissions. Indeed, the statute requires the guidance to include "reasonable timeframes for the Secretary's review of letters, qualification plans, or full qualification packages."[30]

FDA has begun reporting some metrics for its biomarker qualification process.[31] As of October, 2017, the agency reports six instances of biomarkers qualified, although the agency reports at least three of these were qualified before it finalized its 2014 guidance (e.g., these three instances may not have strictly followed the same qualification process as subsequent qualification determinations and, hence, their metrics may not be comparable).[32] As of October, 2017, the types of biomarkers submitted for qualification, from most common to least common, were: Safety, Prognostic, and Pharmacodynamic/Response. There were no biomarkers submitted for qualification as Surrogate Endpoints. Using FDA metrics, as of October 31st, 2017, the average time biomarkers have dwelt in the qualification process, for all biomarkers at any stage, is approximately five and one-half years. Similarly, the longest time for a biomarker to be in the qualification process and still be under Consult & Advice is

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[25] 21st Century Cures Act, Pub. L. No. 114-255, § 3011, 130 Stat. 1033, 1086 (codified as 21 U.S.C. 357(a)(1) (2016)).

[26] CTR. FOR DRUG EVALUATION AND RESEARCH, *supra* note 8, at 7.

[27] CTR. FOR DRUG EVALUATION AND RESEARCH, *supra* note 8, at 7.

[28] CTR. FOR DRUG EVALUATION AND RESEARCH, *supra* note 8, at 8-9.

[29] *See* 21st Century Cures Act, § 3011, 130 Stat. 1090 (codified at 21 U.S.C. 357(b)(1)).

[30] *Id.* at § 3011(b)(1)(B)(ii) (codified at 21 U.S.C. 357(b)(1)(ii)).

[31] *See Current Biomarker Qualification Submissions*, Food & Drug Admin. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm [https://perma.cc/NZB9-F4A6] (last visited Sept. 15, 2017).

[32] *List of Qualified Biomarkers*, FDA (Aug. 5, 2017), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm [https://perma.cc/97RM-LNAW].

reported as just under eight years; while the range of times for biomarkers within the Consult & Advice stage is from this maximum to approximately two and one-half years, with an average time at the Consult & Advice stage of approximately six years. Thus, the fastest time for a biomarker to reach the Review Stage is just over two years.

FDA metrics report only the current stage, out of three stages in the qualification process, for each biomarker submission. These metrics do not report the quality or completeness of submissions or intensity of submitter engagement with the agency. For instance, FDA's reporting does not elaborate further on the submitter's progress towards completing the given stage, such as whether a submitter is simply collecting additional data reasonably required by FDA before then advancing to Review stage; or, for example, whether the submitter has been non-responsive to requests for meetings or information from the agency. No doubt, FDA's recent publication of an evidentiary framework will help provide clarity to submitters and the agency, which should help reduce biomarker qualification time going forward.[33] Still, for many biomarkers, their time in the qualification process is approaching parity with traditional new drug clinical development timelines. For a non-expedited drug program, typically it takes between six and seven years for an innovator to complete all three phases of clinical trials for a novel drug, traditionally from first human dose to final pivotal study and submission of the application.[34] Many of the biomarkers submitted to the qualification program have already been used within one or more proprietary development programs.

External Experts in FDA Biomarker Qualification

FDA guidance concedes that one limitation on its qualification process is "the availability of CDER resources to perform the review";[35] hence, increasing the agency's resources for biomarker qualification would also help improve the timeliness and quality of its operation of this process. We recommend inserting panels of external experts, convened from a suitable partner organization, at the second (Qualification Plan) and third (Review) qualification process stages. FDA would remain the process gatekeeper by retaining its decision whether to accept proposed biomarkers into the qualification process (i.e., the "Letter of Intent" stage), and likewise would retain the regulatory decision-making by having final approval on all submissions.

While one alternative solution is to provide FDA with more funds to expand its headcount, hiring more full-time biomarker qualification personnel, this remedy is not optimal. Inevitably, qualification decision-making requires FDA review division personnel to participate as they are more experienced with the Benefit-Risk determination inherent to qualifying a given biomarker for a COU that is relevant to a disease-state within the purview of their Division. In addition, increasing the agency's payroll may require straining federal resources, exceed hiring limits, or involve budgetary considerations that may be variable from year to year or administration to administration. Further, some biomarkers require specialized knowledge or disease state understanding, and the agency would have to compete with academia or industry to hire and retain these particular experts, who may only occasionally be engaged for

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[33] *See* discussion *supra* note 4.

[34] Pharm. Research & Mfr. of Am. *Biopharmaceutical Research and Development: The Process Behind New Medicines* 10 (May 2015), http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf [https://perma.cc/5WM7-2R4B].

[35] CTR. FOR DRUG EVALUATION AND RESEARCH, *supra* note 19, at 6.

biomarkers falling within their expertise or life-long scientific interest, and these experts would then be less beneficial to the agency on other biomarkers.

II. FDA LEGACY OF USING EXTERNAL EXPERTS

FDA employs leading scientific experts and highly capable leadership, resulting in many of its regulatory processes being rightly regarded as the "gold standard" throughout the world. To remain so distinguished, it is imperative that the agency access key scientific knowledge, given medicine and technology are advancing at a more rapid pace today than at any other time in history. However, in a continuously evolving and cost-constrained world, it is difficult, if not impossible, for any single innovator corporation, academic institution, or government agency to house internally all its needed capacity and expertise. Considering the diversity of needs in executing its public heath mission, this is particularly true for FDA. Hence, for more than half a century, the agency has repeatedly enlisted external experts for both short-term and continuous needs when doing so has improved the timeliness or quality of FDA's operations. In all such cases, the agency has retained its non-delegable agency authority.

Indeed, the agency has a vast history of engaging external experts, notably beginning with the Drug Efficacy Studies (DES). The 1962 amendments to the Food, Drug & Cosmetic Act (FDCA)[36] required all drug products to be FDA approved not only on evidence of safety, as required since 1938, but also on evidence of efficacy.[37] FDA estimated it approved approximately 3,000 marketed drug products between 1938 and 1962[38] which would require review of "real-world" and clinical data evidence, as submitted by their manufacturers, to retrospectively substantiate each marketed drug's efficacy. To complete this massive review, in 1966 FDA requested the National Academy of Sciences-National Research Council (NAS-NRC) form thirty independent panels of at least six NAS-NRC member scientists to complete these Drug Efficacy Study reviews.[39] By 1968 the NAS-NRC panels had completed reviews of over 2,800 drugs as submitted by 237 different manufacturers, with each panel having reviewed an average of 150 drugs.[40] Although the 1962 amendments vested efficacy determination authority with FDA, the NAS-NRC panel reviews provided the agency with a high throughput of recommendations to inform subsequent FDA decision-making as to whether each marketed drug was considered to be effective by qualified experts.

Likewise, FDA turned to panels of external experts for recommendations as to determining the post-1962 amendment efficacy of Over-the-Counter (OTC) drugs. FDA convened OTC review panels to draft active ingredient monographs, which FDA

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[36] Drug Amendments Act of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

[37] *Id*. at 781.

[38] RICHARD A. RETTIG, ET AL., INSTITUTE OF MEDICINE, COMMITTEE TO STUDY THE USE OF ADVISORY COMMITTEES BY THE FOOD AND DRUG ADMINISTRATION, FOOD AND DRUG ADMINISTRATION ADVISORY COMMITTEES 50 (Nat'l Acad. Press ed., 1992).

[39] *Id.* at 50–51.

[40] Warren E. Whyte, *Effectiveness of the NAS-NRC Drug Effectiveness Study*, 25 FOOD DRUG COSMETIC L. J. 91, 93–97 (1970).

finalized via notice and comment process.[41] In approximately 10 years, the seventeen OTC review panels reviewed over 700 active ingredients in hundreds of thousands of marketed OTC products, collectively meeting more than 513 times, with each panel convening over the course of an average of 4.5 years.[42] Still again, in 1972, following transfer of biologic products regulatory oversight to FDA from the National Institute of Health (NIH), FDA convened expert panels to re-examine the efficacy of all licensed biological products which had been previously approved by the NIH. These committees made recommendations to FDA regarding whether reviewed biologic products met the then-contemporary standards for safety and efficacy. Importantly, for none of these review efforts—DES, OTC, or biologics—did the agency first attempt to conduct these reviews internally and then reach-out for assistance; instead, the agency a priori devised these reviews be conducted by external expert panels, and subsequently made independent regulatory decisions from their recommendations.

The Executive branch has urged and occasionally compelled FDA to utilize external experts in similar capacity, most emphatically in the early 1990's through the Council on Competitiveness (the Council), chaired by then-Vice President Dan Quayle. By November, 1991, the Council had recommended eleven different reforms for FDA, including the use of "qualified external review organizations to conduct clinical reviews from those classes of pharmaceuticals where backlogged applications have been pending for more than the statutory period of 180 days."[43] Under the Council's proposal, external experts would first review a sponsor's backlogged application, providing a recommendation to FDA; the agency would retain its final decision-making authority for any application reviewed and retain the right to fully review all data.[44] In April, 1992, at the request of the Council, FDA used discretionary appropriations to contract[45] with Mitre Corporation (Mitre), a not-for-profit, private Research & Development corporation capitalized entirely by the U.S. government.[46] FDA selected and forwarded copies of Supplemental New Drug Applications (SNDAs), complete with supportive data from each sponsor, for five backlogged SNDAs, submitted by their sponsors to expand each drug's approved indication.[47] Although the Council on Competitiveness was terminated on January 22, 1993 by then-incoming President Clinton's administration, Mitre finished reviewing the

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[41] Kenneth C. Baumgartner, *A Historical Examination of the FDA's Review of the Safety and Effectiveness of Over-the-Counter Drugs*, 43 Food Drug Cosmetic L. J. 463, 467 (1988).

[42] *Id*. at 474.

[43] WASH. COUNCIL ON COMPETITIVENESS, FACT SHEET: IMPROVING THE NATION'S DRUG APPROVAL PROCESS 2 (1991).

[44] *Id*. at 3.

[45] Total contract was for $221,608 (1992 dollars), signed on September 24, 1992. *Mitre*, THE PINK SHEET (1993).

[46] In 1996, Mitre Corp. split into two entities: Mitre Corporation to focus on DOD and FAA work; and, Mitretek Systems, now called Noblis Corporation, for all non-DOD/FAA work. Noblis and Mitre Corp. are both classified as a Federally Funded Research and Development Corporation (FFRDC). Kathleen Day, *The Think Tank That Went Out for a Spin; MITRE Splits in Two to Answer Concerns That It Has an Unfair Edge in Government Work*, THE WASHINGTON POST, Feb. 23, 1996, https://www.washingtonpost.com/archive/business/1996/02/23/the-think-tank-that-went-out-for-a-spin/b117b3f3-a72b-44cc-9002fb118d2aadcf/?utm_term=.6f9e17481a79.

[47] *Mitre Third-Party Reviews Resulted in Three of Five Supplements Approved; Two NSAIDs, Two Antibiotics, and One Agent for GERD Are Among the Applications*, THE PINK SHEET (1996).

SNDAs in its queue, completing these reviews by December, 1994.[48] In her 1996 testimony before the Senate, during the Senate's consideration of an FDA reform bill, Dr. Pamela Walker, V.P. of Mitre, related important details of the Mitre review program: "The approximate elapsed time for our review ranged from two months to four months. The approximate cost ranged from $20,000 to $70,000."[49,50] Mitre recommended approval for three of the SNDAs and recommended FDA require the sponsor to submit further data to substantiate the requested changes to the other two drugs' indications.[51] Per Dr. Walker: "The recommendations we made as a result of our reviews were consonant with the actions taken subsequently by the FDA."[52]

Likewise, Congress has repeatedly required and encouraged FDA to use external experts. For example, the "Radiation Control for Health and Safety Act of 1968"[53] required FDA to establish the Technical Electronic Products Radiation Safety Standards Committee (TEPRSSC) which the agency must consult prior to promulgating electronic product radiation regulations.[54] Likewise, the "Medical Device Amendments of 1976"[55] required FDA to use advisory committees to make recommendations on classification of medical devices[56] and provide a recommendation as part of an administrative review process for FDA's approving or denying premarket authorizations (PMAs), declining product development protocols, or FDA revoking or withdrawing approval for a marketed device.[57] Still further, congress, in the Food and Drug Administration Modernization Act of 1997 (FDAMA),[58] directed FDA to accredit persons in the private sector to review certain medical device premarket notifications (510k's)[59] and to provide recommendations on them to the agency.[60] Specifically citing the agency's prior history of external expert driven reviews (e.g., DES reviews), the FDAMA congress encouraged FDA's broad use of external experts to supplement the agency's capacity and capability:

> There are sound reasons for using outside individuals and organizations to review, evaluate, and make conclusions and recommendations to the FDA . . . [i]n some instances, individuals outside the FDA have unique

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48 *Id*.

49 Revitalizing New Product Development from Clinical Trials Through FDA Review: Hearing Before the Subcomm. on the Committee on Labor and Res., 104th Cong. 88 (1996) (statement of Dr. Pamela Walker, Vice President, Mitre Corporation).

50 Approximately $34,000 to $119,000 in 2017 US dollars.

51 *See* source cited *supra* note 46.

52 *Id*.

53 Radiation Control for Health and Safety Act of 1968, Pub. L. No. 90-602, 82 Stat. 1173 (1968).

54 21 U.S.C. § 360kk, *enacted by* Pub. L. No. 90-602, 82 Stat. 1173 (1968); *see also* 21 C.F.R. § 10.80(h).

55 Medical Device Amendments of 1976, Pub. L. No. 94-295,90 Stat. 539 (1976).

56 *See* 21 U.S.C. § 360c, *enacted by* Pub. L. No. 94-295, 90 Stat. 539 (1976).

57 *See* 21 U.S.C. § 360c, *enacted by* Pub. L. No. 94-295, 90 Stat. 539 (1976).

58 Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

59 *See* 21 U.S.C. § 360m, *enacted by* Pub. L. No. 105-115, 111 Stat. 2296 (2016).

60 *See* Food & Drug Admin, *Current List of Accredited Persons for 510(k) Review under the FDA Modernization Act of 1997* (January 11, 2016), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthird party/accredit.cfm [https://perma.cc/2CRJ-J83L].

> expertise not available to the agency . . . [and] the FDA's internal resources are inadequate to handle surges in the workload . . . .
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> . . . .
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> . . . [T]he FDA should wisely and rationally use this authority as a tool to manage an increasing workload in an era of flat or declining resources available to the Federal government, and bring to bear outside expertise when it is helpful.[61]

Further, in the Food & Drug Administration Amendments Act of 2007,[62] Congress required FDA to evaluate all new molecular entity (NME) drug and biologic products via consultation of an Advisory Committee or to provide a justification to the sponsor as to why the agency determined an Advisory Committee review was not required.[63] This same congress also passed provisions enabling FDA to partner with external institutes, to advance its 2004 Critical Path Initiative, which had "the purpose of fostering medical product innovation, enabling the acceleration of medical product development, manufacturing, and translational therapeutics, and enhancing medical product safety."[64] Still further, via the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012,[65] Congress urged FDA to engage external experts for overseeing the development of therapeutics for rare diseases in an *ad hoc* paradigm, a mode of external engagement expanded from the traditional Advisory Committee process, urging the agency to conduct "one-off" consultations with rare disease experts as needed.[66] Continuing the legacy of using external experts, in 2016 Congress passed the 21st Century Cures Act (Cures)[67] which contains several provisions requiring FDA to consult with external experts and stakeholders to implement many novel regulatory science initiatives such as novel clinical trial designs,[68] the regulatory use of real-world evidence,[69] and biomarker qualification.[70] Specifically, regarding biomarker qualification, Cures encourages FDA to "consult with biomedical research consortia

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[61] S. Rep. No. 105-43, pt. iv, at 19–20 (1997).

[62] Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007).

[63] 21 U.S.C. § 355(s), *enacted by* Pub. L. No. 110-85, 121 Stat. 823, (2007).

[64] 21 U.S.C. § 360bbb-5, *enacted by* Pub. L. No. 110-85, 121 Stat. 823 (2007).

[65] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012).

[66] 21 U.S.C. § 360bbb-8.

[67] 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

[68] *Id.* § 3021(b)(3) (Stating "[p]rior to updating or issuing the guidance required . . . the Secretary shall consult with stakeholders, including representatives of regulated industry, academia, patient advocacy organizations, consumer groups, and disease research foundations . . . .").

[69] *Id.* § 3022(c)(3)(A)-(B)., (Stating "[t]he Secretary shall consult with regulated industry, academia, medical professional organizations, representatives of patient advocacy organizations, consumer organizations, disease research foundations . . . through approaches such as a public-private partnership . . . a contract, grant, or other arrangement, as the Secretary determines appropriate . . . .")

[70] *Id.* § 3011.,(b)(3)(A) (Stating: "the Secretary shall, in consultation with biomedical research consortia and other interested parties through a collaborative public process, establish a taxonomy for the classification of biomarkers").")

and may consider the recommendations of such consortia with respect to the review of any qualification plan . . . or the review of any full qualification package . . . ."[71]

FDA Administrative Authority to Use External Experts

Even without congressional or executive requirement, FDA routinely uses several administrative authorities to engage external expertise, including: Public meetings and correspondence; Individual consultations; Advisory Committees; and, contracting with an external organization. FDA may convene a Public Meeting whenever the Commissioner determines "it would be in the public interest to hold an open public meeting to discuss a matter (or class of matters) pending before FDA."[72] The agency typically uses the Federal Register to satisfy its requirements to inform the public of "the time and place of the meeting and the matters to be discussed."[73] Unless FDA specifies otherwise, "any interested person may attend and participate in the discussion without prior notice to the agency."[74] The agency has discretion whether to prepare an official transcript for any Public Meeting,[75] taking into consideration the subject matter of the meeting, the public interest in the issue, and the value of using agency resources to prepare such transcripts, recordings, or memoranda.[76] FDA may likewise exchange correspondence with an interested person outside FDA on a matter within its jurisdiction.[77] As these are informal administrative processes, such consultations are subject to rather minimal provisions and "agency action on meetings and correspondence does not constitute final administrative action subject to judicial review."[78]

FDA may also collaborate with external experts using one of several consultative processes which allow the agency to use single external experts as contracted consultants for defined, and often limited, durations. One prominent process is the use of an Intergovernmental Personnel Agreement as provided by the Intergovernmental Personnel Act (IPA).[79] The IPA allows federal agencies to temporarily assign their consenting personnel to state or local agencies or institutions of higher learning, and vice versa, for periods of up to two years for "work of mutual concern to his [federal] agency and the State or local government that . . . will be beneficial to both."[80] While assigned to a federal agency, the intergovernmental employee must conform to federal

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[71] *Id*. § 3011(a)(2)(D)., (Stating "[t]he Secretary may, for purposes of the review of qualification submissions, through the use of cooperative agreements, grants, or other appropriate mechanisms, consult with biomedical research consortia and may consider the recommendations of such consortia with respect to the review of any qualification plan . . . or the review of any full qualification package . . . .")

[72] 21 C.F.R. § 10.65(b) (1979).

[73] *Id*. § 10.65(b)(1).

[74] *Id*. § 10.65(b)(2).

[75] *See id*. § 10.65(e).

[76] *See* 66 Fed. Reg.FR 14, 6466 – 6467 (Jan. 22, 2001).

[77] *See* 21 C.F.R. § 10.65(a).

[78] *See* 21 C.F.R. § 10.65(a).

[79] Intergovernmental Personnel Act of 1970, 5 U.S.C. §§ 3371-3375 (1971).

[80] 5 U.S.C. § 3372(a)(2).

ethics and compliance requirements as they are "deemed an employee of the Federal agency."[81]

The agency also has contracted with external experts via its own devised processes. In 2011, in order to maintain competency with the innovative technologies in medical devices applications, FDA's Center for Devices and Radiological Health's (CDRH) implemented a Network of Experts (NOE) program to enhance its "rapid access to specific specialized knowledge about emerging technology."[82] Under FDA's NOE procedure, CDRH staff would submit scientific, engineering, or medical questions to external experts, the answers to which are necessary for CDRH staff to effectively complete their work (e.g., reviewing a product application), and for which an existing agency mechanism (e.g., Advisory Committee, Special Government Employees, public meeting, etc.) was inadequate to provide an answer.[83] Experts in the NOE provide scientific consultative services to FDA on a gratuitous basis.[84] The program targets expert access within two weeks of CDRH staff defining a scientific, engineering, or medical question, and anticipates reasonably prompt reply from the experts.[85] In October 2015, FDA's Center for Drug Evaluation and Research (CDER) began operating a similar NOE program.[86] Importantly, no statute compelled the agency to reach out to external experts via the NOE programs; FDA exercised its administrative discretion and kept with its tradition of using external experts to enhance its capacity and capabilities in order to maintain timeliness and quality of its operations.

While more regulated than other consultative processes, the Advisory Committee is a well-known process by which FDA receives independent scientific and medical advice from multiple experts, particularly as to recommendations for approval of a new therapeutic agent or device. FDA Advisory Committees are operated within the legal framework of the Federal Advisory Committee Act of 1972 (FACA).[87] Following the enactment of FACA, and informed by its pre-FACA legacy of using external experts to conduct various reviews, FDA codified its regulations for use of Advisory Committees,[88] setting a very broad discretion for its use of such committees of external experts; theoretically, allowing them anytime "[t]he Commissioner concludes, as a matter of discretion, that it is in the public interest for a standing or ad hoc policy or technical public advisory committee."[89] All Federal Advisory

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[81] *Id*. § 3374(c)(2). Note: exceptions to "federal employee status" are those associated with the employee's health, pension, or leave benefits; *see generally id*. § 3374.

[82] *FDA Outlines Plans for an Outside Network of Scientific Experts*, FDA News Release (Oct., October 4, 2011), http://www.fda.gov.

[83] CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH), NETWORK OF EXPERTS: EXPERT UTILIZATION, STANDARD OPERATING PROCEDURE (Aug. 26, 2015), http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/UCM460028.pdf.

[84] *Id.* at 2.

[85] *Id.*

[86] *See* CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, CDER NETWORK OF EXPERTS, MANUAL OF POLICIES AND PROCEDURES, MAPP 6001.2, (Oct. 23, 2013), http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM469814.pdf.

[87] Federal Advisory Committee Act, 5 U.S.C.S. app. § 1-16 (1972).

[88] *See* 21 C.F.R. § 14 (1979).

[89] *Id.* § 14.1(a)(1).

Committees must file a charter with the General Services Administration.[90] The agency or statute which establishes a given Advisory Committee determines whether committee members are to receive pay and the level of compensation. Per FACA, and unless specified otherwise by statue, Advisory Committee members are reimbursed for their travel, allowed a modest per diem, and paid an hourly rate for their time serving on the committee or when performing specifically-requested, pre-meeting preparation work or analyses.[91] As of this writing, the maximum FDA compensation rate was the base GS-15 step 10.[92] FACA requires that a designated federal officer/employee be assigned to work with each committee, for instance serving as the chair of the committee.[93] To fund an Advisory Committee, Congress may legislate a specific appropriation or it may instruct an agency to use its existing annual appropriation. Congress can also legislate that an Advisory Committee be funded through private-sector donations. Unless statutorily exempted or extended by the President or the agency head, an Advisory Committee automatically terminates two years after its establishment.

FDA establishes an Advisory Committee via notice in the Federal Register,[94] in accordance with Federal Management Regulations.[95] FDA Advisory Committee meeting schedules are published in advance by the agency, and, while certain portions may be closed (e.g., to protect intellectual property), the meetings must include portions which are open and accessible to the public at large.[96] An administrative record is kept of all Advisory Committee meetings, for both open and closed portions, which includes data and records reviewed by the Committee.[97] Advice or recommendations are typically rendered via polling a Committee's voting members on questions presented to the Committee. Panels of experts which advise the agency on scientific matters are often compelled to be classified as Advisory Committees and subject to applicable FACA and FDA administrative requirements. As of January 2016, FDA reports it maintains approximately thirty Advisory Committees.[98]

To further augment its scientific capacity and capability with external expertise, FDA has also contracted with organizations or government entities, such as it did for the DES reviews. Indeed, in 2007 Congress codified the agency's ability to partner with external entities.[99] The agency is occasionally compelled to contract with external experts for a variety of purposes using congressionally approved appropriations or funds; for example, in 2012, FDASIA authorized FDA to retain a third party to conduct

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90 *See* Federal Advisory Committee Act, 5 U.S.C.S. app. § 9(c) (1972).

91 *See* 42 U.S.C. § 217(a).

92 *See* 42 U.S.C. § 210 (c) (approximately $64.00/hour).

93 *See* Federal Advisory Committee Act, 5 U.S.C.S. a pp. § 10(e).

94 21 C.F.R. § 14.40(a).

95 *See* 41 C.F.R. § 102.3.

96 *See* 21 C.F.R. §§ 14.20, 14.25.

97 *See* 21 C.F.R. § 14.60.

98 *See* FOOD & DRUG ADMINISTRATION, COMMITTEES & MEETING MATERIALS, (February 18, 2015), http://www.fda.gov/AdvisoryCommittees/default.htm.

99 *See* 21 U.S.C. § 360bbb-5(a), *enacted by* Pub. L. No. 110-85, 121 Stat. 823 (2007).

a study on drug shortages—specifically the causes, trends, or solutions.[100] In other instances, the agency has initiated external contracting of experts on its own using discretionary funds; for example, in October 2011, FDA awarded $2 million to launch local Centers of Excellence in Regulatory Science and Innovation (CERSI) at the University of Maryland and Georgetown University.[101] FDA's CERSIs are collaborations between FDA and academic institutions to advance regulatory science through innovative research, education, and scientific exchanges.

Preventing Conflicts of Interest

Advisory Committee members and consultants engaged by FDA are subject to laws, rules, and practices designed to prevent or reduce potential conflicts of interest such that recommendations and advice rendered "will instead be the result of the advisory committee's independent judgment."[102] FDA usually classifies external experts it engages as Special Government Employees (SGE).[103] A "Special Government Employee" is a temporary employee in the executive branch of the Federal Government, appointed to perform particular duties for a limited duration, such as serve on an FDA Advisory Committee.[104] The SGE classification applies the same government ethics requirements as applied to other Federal personnel; particularly, with respect to the handling intellectual property or confidential matters,[105] and prohibiting conflicts of interests.[106]

Because scientific experts may be highly specialized, they are often sought by regulated industry and academia alike for their expertise. These experts, if also sought by FDA to serve in an expert consultant capacity, may have financial conflicts of interest. Federal criminal statute prohibits any SGE from participating in an official capacity in matters in which he has a personal financial interest, or in which persons or organizations with which he is affiliated have a financial interest.[107] The statute is intended to protect governmental processes from actual or apparent conflicts of interest that may compromise official action. The statute recognizes that in certain cases (depending on the nature and the size of the financial interest and the nature of the employee's responsibilities), such a conflict may be unlikely to compromise the employee's actions. Thus, waivers of the disqualification provision are allowed, both on a case by case basis and by general regulation. Such waivers must be based on a determination that the disqualifying financial interest is not so substantial as to be deemed likely to affect the integrity of the employee's services to the Government.[108] In addition, waivers are available for conflicts of interest that may arise during service

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[100] *See* Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, 126 Stat. 993 § 1003 (2012).

[101] *See* Centers of Excellence in Regulatory Science and Innovation (CERSI), FDA, http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm.

[102] 5 U.S.C. app. 2 § 5(b)(3) (1972).

[103] 21 C.F.R. § 14.95(a)(1).

[104] 18 U.S.C. § 202(a) (2014).

[105] *See, e.g.,* 21 C.F.R. § 20.20(a).

[106] *See,* 18 U.S.C. § 208; *see also* UNITED STATES OFFICE OF GOVERNMENT ETHICS, LAWS AND REGULATIONS, https://www.oge.gov/web/oge.nsf/Laws+and+Regulations/.

[107] 18 U.S.C. 208(a).

[108] 5 C.F.R. § 2640.301(a)(4).

on an Advisory Committee.[109] For FDA's use of external experts, the Commissioner of Food and Drugs has authority to make determinations in matters such as the issuing of conflict of interest waivers.[110] FDA has a defined process for evaluating potential conflicts of interest prior to making the determination that a waiver is appropriate. This includes multiple independent reviews at various levels of the agency.[111]

III. RECOMMENDATIONS

The most optimal mode of FDA engaging external experts for biomarker qualification is one which maximizes the conservation of agency resources for regulatory decision making based on sound recommendations from the experts. In terms of the qualification process, experts would provide reviews and recommendations of the Qualification Plan and FQP submissions preliminary to FDA decision-making on these reviewed submissions. FDA would most benefit by being able to engage ready pools of such external experts in a flexible mode (e.g., as needed), being able to convene and disband them in keeping with the variable qualification workflow. Just as the agency uses cross-functional personnel to evaluate qualification submissions, the agency would benefit from external experts having diverse scientific disciplines as well as those having relevant therapeutic and disease state experience to review each submission. Optimally, such experts would be able to work together for a limited duration to arrive at a recommendation for a particular biomarker submission. Logically, FDA would also benefit if these experts had some understanding of FDA's approach to benefit-risk decision making to ensure their recommendations are consonant with the weight the agency accords various types of scientific evidence or statistical methodologies. Since qualification's primary purpose is subsequent use of the biomarker COU by therapeutic product innovators to support their R&D, FDA likewise would benefit from experts who have an understanding of the regulatory implications associated with biomarker qualification decisions.

Among the agency's administrative authorities to reach external experts for biomarker qualification, contracting with a suitable consortium would best address these requirements and remedy the agency's resource limitations. Agency meetings and correspondence are effectively included in the existing qualification process and are properly used as means of ensuring access to the agency but are not themselves practical modes of conducting submission reviews. Similarly, engaging one or a few external consultants for each biomarker, while arguably somewhat augmenting the agency's capacity and capability, is again sub-optimal since FDA would still utilize its resources for the initial qualification submission reviews. Similarly, the Advisory Committee process, while appearing to offer a suitable solution, has limitations due to the administrative burden the agency bears for constituting and maintaining each committee.

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[109] 5 C.F.R. § 2640.302(a).

[110] This authority is subject to legal review by the Designated Agency Ethics Official for the Department of Health and Human Services and is allowed in cases where federal law accords the agency authority to exercise discretion regarding such matters. *Policies and Procedures for Handling Conflicts of Interest with FDA Advisory Committee Members, Consultants, and Experts*, FDA, https://www.fda.gov/oc/advisory/conflictofinterest/policies.html.

[111] *Id.*

FDA using a consortium of external experts to conduct the first substantive reviews of the Qualification Plan and FQP would most optimally increase the biomarker qualification process capacity and capability. FDA would remain the gate-keeper, reviewing and approving prospective qualification submission LOIs, then passing the approved LOIs to the consortium partner. The consortium would leverage its ready access to particular experts to review and make recommendations on qualification submissions, sparing agency resources for reviewing such recommendations in keeping with its long-standing mode of leveraging external experts. Several candidate organizations exist; for instance, the Foundation for the National Institute of Health's (FNIH) organization: The Biomarker Consortium (BC). Launched in late 2006, BC is a public-private partnership managed by the FNIH which "endeavors to discover, develop and seek regulatory approval for biological markers (biomarkers) to support new drug development, preventive medicine and medical diagnostics."[112] Founding members include the National Institutes of Health, FDA, and the Pharmaceutical Research and Manufacturers of America (PhRMA).[113] Not surprisingly, BC reports launching more than 20 qualification projects in 13 different disease areas.[114] Similar organizations also include the Critical Path Initiative, the National Academy of Medicine, and the Regan-Udall Foundation. The agency currently maintains relationships or participation with each of these consortia on biomarker qualification matters. Such organizations sufficiently contain, or are able to readily access, scientific and subject-matter experts, particularly those familiar with FDA regulatory decision-making and standards of evidence.

A benchmark external expert supported qualification process is available from Europe. The European Medicines Agency (EMA) has operated an external expert panel biomarker qualification process since 2009.[115] The EMA process is similar to the FDA qualification process in that both are initiated by an LOI and the regulatory authority (EMA or FDA) makes the final qualification decision. Inherent to the EMA qualification process, however, is the use of "a specifically tailored qualification team reflecting the expertise needed . . . appointed to each individual qualification request,"[116] drawn from regulatory organizations (e.g., EMA) "and the larger EU [private sector] experts' network."[117] Public consultation can be included "prior to a final qualification [decision . . . to] ensure that information [is shared] and is open to enlarged scientific scrutiny and discussion."[118] Increasing its regulatory review capacity and capability via external experts, the EMA qualification process contains a timeline with expected submitter and regulatory body responsiveness, theoretically enabling a promised qualification determination within as little as 270 days from EMA receipt of a submitter's LOI.

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[112] *See* FOUNDATION FOR THE NATIONAL INSTITUTE OF HEALTH, ABOUT THE BIOMARKERS CONSORTIUM, https://fnih.org/what-we-do/biomarkers-consortium/about.

[113] *Id*.

[114] *Id*.

[115] Qualification of Novel Methodologies for Drug Development: Guidance to Applicants, European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp.

[116] *Id*. at 5.

[117] *Id*.

[118] *Id*. at 3.

Using a consortium supported qualification process appears to have direct cost benefits for the agency and the submitters. According to one FDA official, biomarker qualification package reviews could require FDA resources "similar to a review of a drug application with clinical data—about $1.3 million to $2.3 million per biomarker."[119] This extreme estimated cost would seem to create disincentives for both the agency and submitters, but is perhaps based on FDA operating the entirety of the qualification review effort. Since at least FDAMA 2007, drug application review user fees have included costs for the agency to maintain Advisory Committees to review sponsor applications. While one can hypothesize costs for using external experts to review biomarker qualification submissions based on the Advisory Committee requirements as a benchmark,[120] the costs for FDA to convene Advisory Committees to review applications since FDAMA 2007 are logically a fraction of a new drug user fee.[121] Nevertheless, even in using consortia to qualify biomarkers, FDA staff resources would be required to make decisions on the qualification submissions. However, just as for the DES, OTC, and Mitre reviews, external experts would lower the agency's overall costs and increase capacity as FDA would be acting on pre-screened submissions, endorsed by a third-party committee of subject matter experts, allowing FDA to more efficiently execute regulatory decision making. In fact, as recently as July 2015, FDA biomarker qualification leadership stated support for a hypothetical external expert-supported qualification process, where external experts would "conduct substantive reviews and make [qualification] recommendations to FDA."[122]

Further Considerations

As was the case in establishing the DESI, OTC, and Biologics reviews, the agency would have to complete some work to ensure successful use of a consortium-supported qualification review process. As a preliminary matter, the agency would have to articulate the roles and responsibilities for the external expert consortium within the biomarker qualification process by amending its guidance document.[123] Indeed, this document could be improved by amending it given 21st Century Cures' biomarker provisions. Stakeholders would also benefit from a public statement of agency intent,

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[119]Derrick Gingery, *Biomarker Qualification Costs as Much as Application Review, FDA Says*, PINK SHEET DAILY, (May 20, 2015)

[120]For instance, assuming a hypothetical 12-member external expert qualification team, meeting for three days, with each attendee having average travel and per diem costs of $2500.00, being paid the maximum listed FDA hourly rate for comparable Advisory Committee members ($69.00/hour times 8 hours = $552.00/day), with the qualification requestor renting a facility to host the committee meetings ($1000.00 per day): (3 days)(12 members)($552.00/day) + (12)($2500.00) + (3 days)($1000.00) = $52,872.00 per meeting. Assuming the Committee meets twice before positively recommending the IBP and once to recommend on the FQP (9 total days of meetings for 12 members traveling to 3 meetings) = (3 days) ($52,872.00) = $158,616.00 in Advisory Committee qualification costs. For FDA estimated cost of $1.3 million, the hypothetical 12-member advisory committee could meet for over 73 days, traveling to 24 separate meetings, each of 3 days' duration.

[121]A detailed economic analysis is outside the scope of our paper.

[122]S Amur, et al., *Biomarker Qualification: Toward a Multi-Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization,* 98 CLINICAL PHARMACOLOGY AND THERAPY CLIN. PHARMACOL. THER. 34, 45 (2015).

[123]*See* source cited *supra*, note 8.

clearly communicating the intended forward-path and a time to implement this process change.

Regardless of the source of the external experts, the nature of biomarker qualification mitigates their potential conflicts of interests, although the agency can further confirm this. The underlying question in examining a potential conflict of interest is whether the expert's prospective financial interests are substantial enough to affect the integrity of the expert's services. Assuming the federal conflict of interest statute[124] applies to a contracted external expert qualification consortium, the nature of a supposed conflict of interest in biomarker qualification may be far too remote. First, the resulting product of biomarker qualification approval is an opportunity to use the marker's approved COU by any innovator; there is no private ownership of this newly created opportunity. Second, similar to other agency uses of outside experts, the proposed biomarker qualification process retains FDA oversight and ultimate approval. Qualified biomarkers lend monetary value to future therapeutic innovators who may use the qualified marker without costly testing needed to re-confirm their COU. However, those future innovators must still receive independent FDA approval for any therapeutic product relying on a qualified biomarker's COU. The financial incentives for biomarker qualification are highly speculative given the non-proprietary nature of the qualification effort and the need for FDA to independently approve both the qualification and any product application which might (or might not) be able to utilize the qualified COU. Indeed, it is hard to compare the nature of any conflict of interest for external experts reviewing biomarker qualification submissions versus similar experts, for instance, convened on an Advisory Committee making market-access recommendations for a specific therapeutic product benefitting a discrete number of proprietary sponsors. Even assuming a conflict exists in qualification reviews, FDA can address any potential conflict of interest concerns for individual biomarkers using its well-documented and thorough process for assessing whether a waiver is appropriate in a given case. Nevertheless, FDA and the Office of Government Ethics should investigate identifying and handling potential conflicts of interests, if there are any.

In addition, the agency would require funds to establish and to maintain a consortium-supported biomarker qualification process. To establish the consortium supported qualification process, FDA has available its 21st Century Cures Innovation Account.[125] To ensure robustness of submissions into the qualification process and to reimburse consortia for their experts' time, one solution would be to charge a reasonable fee to a qualification submitter. A suitable estimate of such fee could be informed from FDA's DES, OTC, or even the Mitre reviews. As a corroborating benchmark, the EMA external expert leveraged biomarker qualification process charges submitters a relatively modest fee for initial qualification attempts,[126] with half

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[124] *See* 21 U.S.C. § 208.

[125] The 21st Century Cures Act (*see note 8, supra*), Title I, section 1002 establishes an "FDA Innovation Account" for Fiscal Years (FY) 2017 – FY 2025 and authorizes funding, subject to the annual appropriation process, to be used by FDA to implement provisions in Title III of the Cures Act. Qualification of Drug Development Tools, which include biomarkers, is in Title III, sec. 3011.

[126] 82,400.00 Euro, or approximately $110,000 USD in 2016 dollars; *see Explanatory note on fees payable to the European Medicines Agency*, EUROPEAN MEDICINES AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp

this fee for any re-submissions or further advice. Congress would have to amend the FDCA to enable the agency to collect any such qualification fees.

To help determine further considerations, FDA should initiate a small-scale pilot of a consortium supported qualification process, using its Innovation Funds.[127] In this pilot, the agency could select one or two current biomarker IBP's from submitters willing to participate. A partner consortium would convene panels of appropriate experts to meet with the submitters and determine the sufficiency or any recommendations on the submitters' IBP's (now "qualification plans" under 21st Century Cures). This pilot could also test the consortium's application of FDA's evidentiary considerations as well as implementing a transition to the new statutory qualification process. The pilot would further inform the agency on the operational costs and savings in using external experts, which could help compute a reasonable cost to establish a consortium-supported qualification process, including any proposed qualification fee, if necessary. The pilot could also help FDA establish timelines for the qualification process, the improved predictability of which would potentially attract more qualification investment.

CONCLUSION

Although the use of external experts would be most enhancing to FDA biomarker qualification process following the articulation of evidentiary requirements, the groundwork to contract with a consortium can be commenced now, and can be implemented following articulation of the evidentiary requirements. FDA is responding to the calls from public and private sector stakeholders, and deserves much commendation for its difficult work on establishing a biomarker qualification process and articulating evidentiary requirements. These efforts are timely. In 2015 and in 2016, the Obama administration announced the ambitious Precision Medicine Initiative[128] and the Cancer Moonshot,[129] both of which will rely on biomarkers to help herald tomorrow's targeted therapies. The agency has already been strategically partnering with experts on biomarker qualification. Likewise, since the Fall of 2015, the agency has partnered with the NIH, Critical Path Institute, and Biomarkers Consortium to establish further elements of its biomarker qualification process, producing a biomarker glossary,[130] and announcing public workshops to develop a framework which supports subsequent FDA guidance on evidentiary requirements for qualifying biomarkers.[131] Amidst this progress and calls for action, FDA has another opportunity readily accessible to it for further refinement of its biomarker qualification

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[127] *See* Amur, *supra* note 121, at 35.

[128] *See* NATIONAL INSTITUTES OF HEALTH, ALL OF US RESEARCH PROGRAM, https://www.nih.gov/precision-medicine-initiative-cohort-program (last visited Oct. 28, 2017).

[129] *See* Office of the Press Secretary, FACT SHEET: Investing in the National Cancer Moonshot, The White House, (Feb. 1, 2016), https://www.whitehouse.gov/the-press-office/2016/02/01/fact-sheet-investing-national-cancer-moonshot.

[130] *See* FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, http://www.ncbi.nlm.nih.gov/books/NBK326791/.

[131] *See* Developing an Evidentiary Standards Framework for Safety Biomarkers Qualification Workshop, http://www.cvent.com/events/developing-an-evidentiary-standards-framework-for-safety-biomarkers-qualification-workshop/event-summary-5fa12cd5dd0e45d0b5ed6f484c22299b.aspx.

process: leveraging external experts through a suitable consortium to increase its capacity and capability for biomarker qualification.