

### The Honorable Gus Bilirakis

- 1. One mechanism drug companies have to improve certainty about the Agency’s acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract.**

Special Protocol Assessments (SPAs) are agreements between the FDA and trial sponsors regarding the protocol design, size, and endpoints of a particular trial. SPAs are desirable because they provide sponsors with increased confidence that the FDA is satisfied with the design and execution of a trial, and can ensure that sponsors receive a timely response to questions that they may have during the development of a new product. However, the FDA does have the right to rescind a SPA if public health concerns become evident that were not recognized at the time the SPA was reached. It is up to trial sponsors to disclose publicly whether they have obtained a SPA agreement with the FDA, so not all such agreements are known. The FDA does release the number of requests for SPAs it receives.

#### Requests to FDA for SPAs<sup>1</sup>

Year	2008	2009	2010	2011	2012	2013
# of SPA Requests	354	336	309	313	288	220

An analysis conducted by the market research firm PROPTHINK concluded that “sponsors who have successfully conducted studies that have met the predefined outcomes in a SPA agreement are highly unlikely to be rejected on the grounds that more clinical data/studies are required.” In addition, the analysis noted that “a successful SPA-backed NDA does not guarantee approval on the first regulatory review cycle.”<sup>2</sup> Thus, SPAs increase the likelihood that the FDA will evaluate efficacy and safety data without raising objections to elements of trial design, but that does not guarantee that the efficacy and safety data will be robust enough to support approval.

In the field of cancer, there are several examples of drugs receiving SPAs and being subsequently approved: Onyx Pharmaceuticals’ Kyprolis for multiple myeloma received a SPA in 2010 and was approved in 2012; Abraxis’ Abraxane for non-small cell lung cancer received a SPA in 2007 and was approved in 2012; Gloucester’s Istodax for a rare lymphoma received a SPA in 2007 and was approved in 2009; Seattle Genetics’ Adcetris for Hodgkin lymphoma received a SPA in 2010 and was approved in 2011.

<sup>1</sup> FDA Prescription Drug User Fee FY2013 Performance Report: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384035.pdf> Accessed 6/12/14

<sup>2</sup> Special Protocol Assessments: The Case Studies: <https://propthink.com/special-protocol-assessments-a-case-study/> Feb 22, 2013. Accessed 6/12/14

An example of a drug that received a SPA but was not approved due to an unfavorable risk/benefit profile was Ariad's ridaforolimus for soft tissue sarcoma. In this case, even with the confidence from the FDA in the trial design, during further testing the drug was shown to have significant risk for kidney and heart problems, with marginal potential benefit.

**2. For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate endpoints that are reasonably likely to predict clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can the FDA work with stakeholders to determine new endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?**

Accelerated Approval, as codified in the 2012 FDA Safety and Innovation Act, is the approval of a drug based upon its effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.<sup>3</sup> It has been an extremely useful tool for the FDA to bring therapies to patients for serious conditions, as has shown especially instrumental in looking at therapies that treat HIV and different forms of cancer.<sup>4</sup> While it is a requirement for a drug approved under Accelerated Approval to treat a serious or life-threatening illness, a key reason that Accelerated Approval has been used more frequently in the cases of HIV and cancers is due to the availability of surrogate endpoints that have been demonstrated to be likely to predict a clinical benefit – such as viral load reduction and tumor shrinkage, respectively. Conversely, there are other disease settings where an endpoint other than overall survival has been so clearly correlated to clinical benefit that it would no longer be characterized as a surrogate, and full approval could be granted based upon a favorable improvement to that endpoint measure (without the post-market commitments of an Accelerated Approval). An example of this is a drug effect on lowering cholesterol in the blood as a predictor of improved heart health.

In all of those cases (cancer, HIV, heart disease) research on the intermediate endpoints was needed to help correlate the surrogate to positive clinical outcomes. FDA has historically encouraged new research to identify potential intermediate endpoints and recently developed programs such as the Biomarker Qualification program to help provide input from the agency into on-going research programs seeking to validate new endpoints.<sup>5</sup> The FDA is quite receptive to working with stakeholders interested in researching potential intermediate endpoints. Additional resources for the agency could help expand this work, since often times, due to funding and personnel constraints, advancing new regulatory programs are difficult to execute with the many significant core responsibilities of agency staff. A

---

<sup>3</sup> Food and Drug Administration Safety and Innovation Act PL 112-144 Sec. 901.

<sup>4</sup> Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. *J Natl Cancer Inst.* 2011;103(8):636-44. Epub 2011/03/23. doi: 10.1093/jnci/djr062. PubMed PMID: 21422403

<sup>5</sup> FDA Biomarker Qualification Program:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm> Accessed 6/13/14

coordinated effort by experts throughout biomedical research community could; help identify which endpoints in different diseases should be of the highest priority, collaborate with FDA to design the appropriate studies for attempting to correlate biomarker candidates to clinical outcomes, and focus resources toward conducting those studies.

**3. What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?**

Most medical records and health data collection systems were not set up to have research as a primary function. Instead, they were developed to process payment for services provided or to provide a record for a single person, at a specific office or center, without the intent or ability to aggregate data from a population standpoint. Some of these barriers have been reduced over time with the advancement of health IT and the implementation of new technology in different care settings or by different care providers and insurers. However, there are still numerous restrictions on how data can be collected and aggregated with privacy concerns frequently cited as a key barrier.

While misuse of data for discriminatory purposes is critical to prevent and patient privacy protections must remain vigilant especially as more data is being generated on each person today than ever before. This provides new opportunities for empowering people to be more active in their care, have access to their health information, and create ways in which research can be conducted in different ways without having to necessarily be a part of a clinical trial. For example, patient data no longer needs to only be collected during periodic doctor visits. Today, many consumers employ technologies to track their daily health for their own personal knowledge. This type of information, while perhaps not as rigorous as full medical exam, can provide longitudinal data about how a medical intervention may be affecting daily activity, provide a way for people to record their direct experience with a medication as it's happening, and help optimize appropriate use of medication. Streamlining different technologies and developing ways for them to interact with a central, interoperable health record with the appropriate, but not unduly burdensome, privacy protections could create new ways for generating health data in the real world.

**4. Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leverage for supplemental applications?**

Collecting and utilizing data about a drug's effect in a disease setting outside of the initially approved indication is an important part understanding the full and optimal use of a drug. This can be done in the context of a formal clinical trial or through additional monitoring of off-label use of a drug. In some

cases of Accelerated Approval where a drug is granted an initial approval in one type of cancer and the required confirmatory studies are actually conducted in a different subset or type of cancer. Not only has this confirmed the initial studies of the drug, but it can lead to an expansion of the label and provide benefit to a broader group of patients. This is one confined example that would use a formal clinical trial as the data source for developing a growing body of evidence about a drug, but perhaps some common principles can be applied.

A major challenge in using real world data is collecting data for patients being treated with a therapy off-label. Registries are frequently established to collect specific information about the effect of a drug outside of a clinical trial. However, while registries are less resource intensive than a typical clinical trial, there are limitations to the conclusions that can be made based on observational data. It could be useful to prospectively work with a wide variety of stakeholders to define what data would need to be collected in the form of a registry that could facilitate a regulatory decision on the supplemental use of a drug. This would likely need to be evaluated on a case by case basis, but it could be an available option for expanding the use of a drug in some cases, particularly when the safety profile of the drug is well understood.

While this could provide one option for generating additional data without the challenge of conducting a clinical trial after the drug has been on the market, it does not alleviate the challenge of tracking off-label use more generally without the proactive intent for expanding the label of the drug.

**5. As a Member of Congress, we hear tales about how companies meet with FDA on drug approval, and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science.**

Scientific advancements are occurring at an increasingly rapid rate. In order to fully capitalize on prior investments in research and development, all components of the biomedical research enterprise need to keep pace or they otherwise risk becoming a limiting step that could slow progress in health care. Like any physician is expected to keep up on the latest advances in science so they can treat their patients with the most effective therapies, FDA scientific review staff needs to continually learn about and be involved in cutting edge science. The FDA's current budget often times hinders this vital education from occurring, which could leave the FDA a step behind the science. One example of this is limited travel budgets for agency officials to participate in scientific meetings. Annual meetings of professional societies and other significant conferences that address key issues among the regulatory and scientific communities provide venues for the most recent scientific and clinical advancements to be presented and discussed. If FDA officials are to advise on the development and review marketing applications regarding the most advanced scientific discoveries they need to be involved in the robust scientific discussions and debates that facilitate their development.

**The Honorable Jan Schakowsky**

- 1. A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new Hepatitis C drug treatment costs about \$100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation**

Advancements in medicine and the development of new drugs won't achieve their intended benefit if patients can't access them. The passage and implementation of the Affordable Care Act provides the opportunity for millions of Americans that previous had no health insurance to obtain coverage. The terms of coverage and the benefits that it provides will continue to be examined as the exchanges expand enrollment, and states adapt to this new law. It will be important to look a variety of factors that still may impede access to such transformational treatments. For example, if the co-pays associated with specialty drugs like those associated with treating illnesses like Hepatitis C, results in a patient out-of-pocket cost so high that it is causing significant limitations for people that need these drugs, then re-examining cost sharing structures may be necessary. This is a different issue than the proposed base price of the drug, but it may be an actual point where access is limited. Whether a drug costs \$100,000 per year or is reduced by ¼ to \$75,000 per year, if the co-pay originally associated with it was unaffordable to the patients it's likely that the co-pay will remain a barrier to access regardless of the price of the drug. Price negotiations, like those that take place between private sector payers, VA hospitals, and others, but not between CMS and companies, could be further evaluated.

This is just one example of how shared cost structures may need to be examined. It is not meant to be rationale for any unjustified pricing, but rather an acknowledgement that realistic out-of-pocket costs and cost sharing strategies may need to be examined, and that all stakeholders are going to have to play a part to ensure that patients have access to new medicines that can improve their lives.

- 2. Advocates often work with Members of Congress to request that FDA develop Guidance Documents in an effort to spur discovery and innovation for various diseases. Would you discuss the importance of Guidance Documents to accelerating the drug development process? In your opinion, is the FDA doing a sufficient job in developing Guidance Documents? What can Congress do to increase the production of these important documents?**

FDA Guidance documents provide the research community with up to date information about agency requirements, current policies, and potential approaches to drug development. While many decisions need to be handled on a case by case basis, these documents provide a framework for establishing the

different parts of a drug development and research program and help inform future interactions with the FDA. Specifically, FDA has used guidance documents as a way to effectively communicate with researchers and companies about new strategies for drug development such as co-developing a drug with a companion diagnostic<sup>6</sup>, use of novel endpoints like pathologic complete response in breast cancer<sup>7</sup>, or developing novel combinations of drugs to treat serious illnesses.<sup>8</sup>

FDA's ability to develop new guidance documents are limited by resources, time, and available personnel. Under these circumstances, FDA has been consistent in issuing Guidance documents from year to year, but with additional resources more Guidance documents could be developed, and with increased ability to interact with experts across the biomedical research community, more robust and forward-thinking guidance could be developed<sup>9</sup> Congress should increase the base funding for FDA to give the agency a greater ability to prioritize the development of Guidance documents, many of which may be outside the scope of programs to which user fees are able to be applied. Establishing a process that would allow external input regarding potential subjects for future guidance documents could also be a helpful way of ensuring that FDA fully realizes the components of drug development that researchers are challenged by most and identify areas where additional guidance documents may be useful.

- 3. I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIG is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIH means to the pace of drug innovation? How has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?**

---

<sup>6</sup> FDA Guidance: In Vitro Companion Diagnostic Devices.

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf> Accessed 6/19/14

<sup>7</sup> FDA Guidance: Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf> Accessed 6/19/14

<sup>8</sup> FDA Guidance: Codevelopment of Two or More New Investigational Drugs for Use in Combination:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf> Accessed 6/19/14

<sup>9</sup> FDA Drugs (Guidances):

<http://www.fda.gov/Drugs/GuidancecomplianceRegulatoryInformation/Guidances/default.htm> Accessed 6/19/14

Thank you for your on-going and steadfast support for funding of biomedical sciences and NIH, it is greatly appreciated. Without champions for research like you much of the progress that has been made to date would not have occurred.

NIH funding is the engine that drives discovery and a key reason that we are currently seeing many scientific advances today. However, as you described over all purchasing power continues to decline. This has the ability to slow the pace of innovation because it simply will take longer to conduct the many potentially transformative research projects that will have to be postponed until funding becomes available. One example in cancer is an NCI initiative called The Cancer Genome Atlas (TCGA). Since the project began in DATE, about 30 different tumor types have been genomically sequenced to provide cutting-edge information about cellular alterations that may be driving cancerous growth in those tumors.<sup>10</sup> With additional resources, more tumor types could be analyzed. The results of these advanced analyses help to identify targets that drugs can be designed toward and potentially stop the cancerous growth. These early studies serve as the foundation for innovative drug development and projects like the Lung-MAP trial, a public private partnership that we spearheaded this past week that will simultaneously test multiple drugs that are targeted toward different molecular alterations.<sup>11</sup> Lung-MAP is designed to address several current challenges in clinical trials and has the ability to improve enrollment, enhance consistency, increase efficiency, reduce costs, and most importantly - improve patients' lives. The design of Lung-MAP utilized the results of TCGA analysis of squamous cell lung cancer. This example of accelerating the pace of innovative drug development could not occur without the strong foundation of knowledge only possible through robust NIH funding. Continued erosion to NIH purchasing power will limit the number and delay the pace at which these stepwise research projects can be conducted, leaving patients to wait for potentially life improving products stuck in the pipeline.

In addition to the direct consequence in delayed development, reduced purchasing power brings long term damage to the biomedical research enterprise. Decreased purchasing power has caused a reduction of scientists that are able to continue their careers in research. Perhaps more detrimental is that has discouraged young talent from considering research as a viable career option and forced them to focus their talents into other fields. The average length of time from graduating high school to completing a doctorate degree in the life science is approximately 11 years (for students that go directly from a bachelors program through doctorate).<sup>12</sup> If the number of young scientists going into life sciences declines, even if NIH funding were to be restored to prior levels of purchasing power, it will take over a decade to reverse the trend in a diminished workforce to develop new medicines.

---

<sup>10</sup> National Cancer Institute, The Cancer Genome Atlas: <http://cancergenome.nih.gov/cancersselected> Accessed 6/19/14

<sup>11</sup> Lung-MAP: <http://www.lung-map.org/> Accessed 6/19/14

<sup>12</sup> National Science Foundation, Higher Education in Science and Engineering: <http://www.nsf.gov/statistics/seind12/c2/c2s3.htm> Accessed 6/19/14

**The Honorable H. Morgan Griffith**

- 1. What legal barriers currently exist that limit the potential for doctors, researchers and drug companies to communicate on how therapies are working for patients in the real world? What can we do to break down some of those legal barriers that are preventing reasonable and valuable treatments from getting to the patient?**

Due to advanced information systems, more data is being generated in healthcare than ever before. This presents new opportunities for improved learning about outcomes on a broad population level and for developing new methods for conducting research. The Health Insurance Portability and Accountability Act was passed in 1996 to protect patient privacy regarding health records. It has yielded important steps to help protect privacy and raise awareness about the need for privacy measures. However, in today's growing electronically-based systems it may present barriers to fully capitalizing on research using data generated in healthcare. The existing privacy rules can prevent researcher from accessing large numbers of patient records to evaluate the safety and efficacy of new drugs outside of clinical trials or to conduct other research activities, such as assessing long term data about different interventions.

In the case which is drug is being used in an off-label setting, companies are restricted from communicating any benefits associated with its use to prevent general promotion of drug for uses other than those for which they are FDA approved. While these restrictions were put into place to help prevent misinformation reaching consumers, there are situations where emerging characteristics of a drug have been made clear through real world use of a product and that information may not be formally put into the label. In a non-promotional way, consumers could benefit from knowing additional information about a drug they're considering or already taking before having to wait for a formal label updating process before the information can be communicated.