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21st Century Cures Initiative & Examining PCAST

to Advance Developing Medicines for Americans

Thank you for this opportunity to provide input on several important PCAST recommendations that may have implications for the 21st Century Cures initiative. As a member of the Board of Directors of the National Organization for Rare Disorders (NORD), and because I have a rare autoimmune disease for which there is no approved therapy, and because none of the approved therapies for Tourette Syndrome work for my son Tom, I am reminded daily that the 30 million Americans affected by rare diseases as well as all of our families have a vital and urgent need for faster development of therapies for each of “us.” In addition to my more than three decades of experience in drug regulation, I was involved with the President’s Council of Advisors on Science and Technology (PCAST) report that is being discussed today. With that as background, let me present you with 4 proposals for the Committee and Subcommittee to consider as you move forward with your 21st Century Cures initiative.

The 21st Century Cures “Call to Action” states that one way for Congress to reach its objective of helping to accelerate the discovery, development, and delivery of promising new treatments is for Congress to ensure that existing statutory and regulatory authorities are being

used to their maximum potential. Toward meeting this objective, I present 4 proposals that build on recommendations in the PCAST report and which the 21st Century Cures initiative could consider using to propel drug development and yield, both quickly and with little new effort, great benefits for patients. While new, more explicit statutory authority from Congress could direct FDA to adopt these (or other) concepts, the Agency, under current law, has sufficient authority to accomplish these things now. However, this Committee and your 21st Century Cures initiative still has a vital role to play in that this Committee has the power to assure FDA that its or the Agency's expanded exercise of existing authorities, as I propose, is encouraged by both sides of the aisle. This is because the PCAST and my proposals for expanded use of current authorities is quintessentially bipartisan in that those suffering with disease are, first and foremost, patients in need of that help, and disease has no political affiliation or partisanship.

Proposal #1: Increase the Visibility and Use of Accelerated Approval by Considering it for Each New Therapy.

Both PCAST and FDASIA recommended that FDA expand, beyond cancer and AIDS, use of its Accelerated Approval authority to approve medicines for those with serious diseases and no available therapies. My September 2013 analysis of the 19 therapies approved since 1992 (when FDA created Subpart H) shows that FDA has already been exercising considerable, reasonable flexibility in using this approval authority. This means that to implement the PCAST and FDASIA recommendation to use this authority more often, FDA would not need to establish any new program or policies, but may only need to give this approval pathway more visibility and more frequent consideration. My first proposal is that Congress encourage FDA to adopt a practice of considering the appropriateness of its Accelerated Approval authority for each new therapy. One way to accomplish this would be to have FDA and a sponsor consider whether that therapy could be a candidate for this approval pathway at one or more key FDA Sponsor

meetings such as pre-IND, End-of-Phase 2, pre-NDA/BLA and Advisory Committee meetings. This simple change would require nearly no resources or time, but could have a huge impact on Americans' access to medicines for serious diseases. Also, see Proposal #3 below.¹

The PCAST report recommends that FDA use more often FDA's existing Accelerated Approval authority, what is also known as Subpart H or Fast Track. The PCAST report noted that 87% of Subpart H approvals had been for cancer, HIV or anthrax. Since 1992, only 21 therapies have been approved via Accelerated Approval authority were for indications other than cancer or HIV.

Specifically, the PCAST report stated:

"The FDA should make fuller use of authorities previously granted by legislation and not yet fully utilized. The FDA should expand the use in practice of its existing authority for Accelerated Approval. FDA should direct its staff, across all divisions, to make full use of the Accelerated Approval track for all drugs meeting the statutory standard of addressing an unmet medical need for a serious or life threatening illness and demonstrating an effect on a clinical endpoint ... or on a surrogate endpoint that is reasonably likely to predict clinical benefit."²

At about the same time as the PCAST report,³ Congress and President Obama in FDASIA recognized the need for expanded use of the Accelerated Approval pathway and revised the statutory provisions of Accelerated Approval to "encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."⁴

¹ A chart is proposed which is attached as Appendix 1.

² PCAST Report at p. 61 (emphasis added).

³ The PCAST report issued in September 2013 and FDASIA became law in July 2013.

⁴ Federal Food, Drug, and Cosmetic (FDC) Act § 506(e)(1).

In June 2013, FDA released its *Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics* (Draft Guidance). The Draft Guidance lists and describes factors that FDA views as critical to Accelerated Approval.

Given this renewed recognition of the promise of FDA’s Accelerated Approval authority to address those suffering from serious diseases without adequate available therapy, and given FDA’s issuance of its Draft Guidance addressing the Agency’s Accelerated Approval authority, my colleague Alexander Varond and I conducted an analysis of FDA precedents in order to promote a better understanding of the circumstances under which Accelerated Approval may be employed in order: (1) to facilitate the development and expedited review of new drugs with the potential to address unmet needs for serious and life-threatening illness; and (2) to mobilize expanded use of Accelerated Approval, consistent with PCAST and FDASIA.

The linchpin of the Accelerated Approval authority is the concept that a showing on a surrogate or intermediate clinical endpoint (ICE) may be sufficient for meeting the statutory criterion or standard of “substantial evidence” of effectiveness.

There have been many misunderstandings, in my view, of this Accelerated Approval authority. Some have thought that this means that the quantum or quality of evidence was somehow reduced, and the statutory requirement of “substantial evidence of effectiveness” was in some way, in whole or in part, reduced, skirted or deferred. While this is not the case in statute, regulation or policy, the other extreme is just as likely not to “serve the public well.”⁵ The other extreme is the view that unless the surrogate is validated, it cannot be relied upon in an Accelerated Approval decision. This is sometimes found in FDA reviews that conclude that the Sponsor’s evidence failed to satisfy the standard of approval because the trial(s) attempted to

⁵ PCAST Report at p. 59.

both prove the drug’s effect on the surrogate as well as prove the clinical benefit, and the clinical benefit showing was not robust enough to confirm or validate the drug’s effect on the surrogate.

Between these two extremes, there has existed a gaping hole that has begged to be addressed for nearly three decades and that hole is this:

- What is the foundation for FDA’s determination that the evidence of effectiveness is capable of supporting an Accelerated Approval?

My colleague Alexander Varond and I reviewed, based on examination of publicly available information, the strength of the scientific and clinical evidence for evaluation of the particular factors that the FDA considers in approving a drug under its Accelerated Approval authority. Our analysis showed that FDA has exercised considerable flexibility in the therapies it has approved under Accelerated Approval.⁶ In all, 19 non-AIDS, non-cancer Accelerated Approvals were identified and analyzed. AIDS and cancer therapies were excluded from the analysis because there is comparatively greater regulatory certainty associated with Accelerated Approvals for these two therapeutic areas.

Our study was designed to assess the evidentiary foundation for FDA’s determinations that an unvalidated surrogate or clinical endpoint was “reasonably likely to predict” patient benefit sufficient to meet the statutory standard of “substantial evidence of effectiveness.” Let me explain how we conducted this analysis.

The FDA’s June 2013 Draft Guidance identified the following as the three most important factors in FDA’s reaching its Accelerated Approval decisions: (1) understanding of

⁶ E-Filing on Regulations.Gov by Frank Sasinowski and Alexander Varond, Hyman, Phelps & McNamara, P.C. re: Docket No. FDA-2013-D-0575, Comment on Section VII. C.: “Evidentiary Criteria for Accelerated Approval” of the FDA “Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics” (Aug. 26, 2013), available at <http://www.regulations.gov/contentStreamer?objectId=09000064813ca6cb&disposition=attachment&contentType=pdf> (Appendix 2). Manuscript in development for publication with update that will expand the analyses.

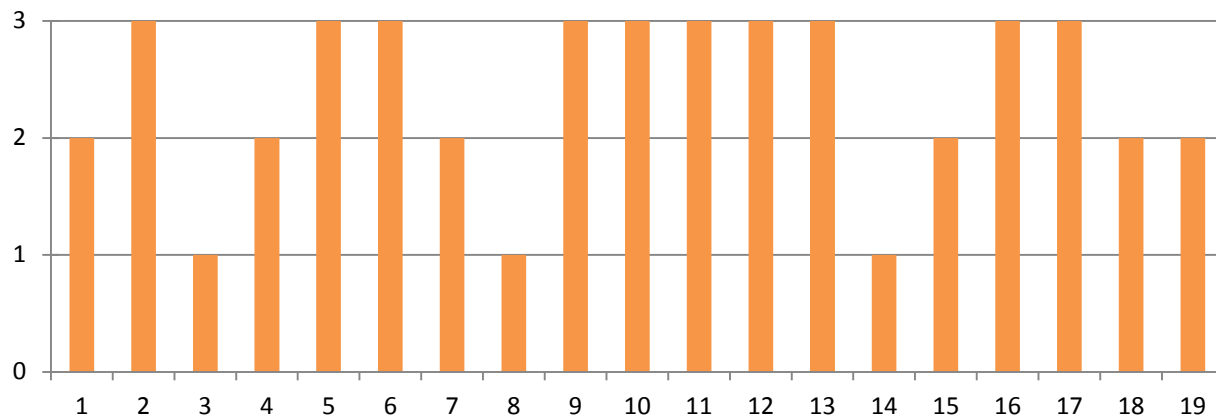
the disease process; (2) understanding of the relationship between the drug's effect on the surrogate or ICE and the disease; and (3) strength of clinical evidence, with strength of clinical evidence broken into two subcategories: strength of clinical evidence on the surrogate endpoint or ICE, and strength of clinical evidence on the clinical benefit.

Our study analyzed all the relevant FDA reviews according to each of these 3 factors. What now follows is a summary of the findings of our analysis, broken down according to those 3 major FDA factors.

The first factor is the understanding of the disease, because, as FDA explains, a clear understanding of the pathophysiology of the disease process will facilitate reliance upon a surrogate or ICE.⁷ However, our analysis found that the absence of a complete understanding of the disease process or even the existence of a relatively weak understanding of the disease process is not, in and of itself, incompatible with an FDA decision to grant an Accelerated Approval. So, with respect to the application of this factor that FDA identified as critical to its decision on Accelerated Approval, FDA exhibited flexibility, according to the findings of our analysis, in applying this consideration to the evidence presented. Figure 1, below, illustrates the strength of FDA's understanding of the disease process for each of the 19 drugs.

⁷ Draft Guidance at pp. 18-19, lines 617-648.

Figure 1: Understanding of the Disease Process (0-3)*

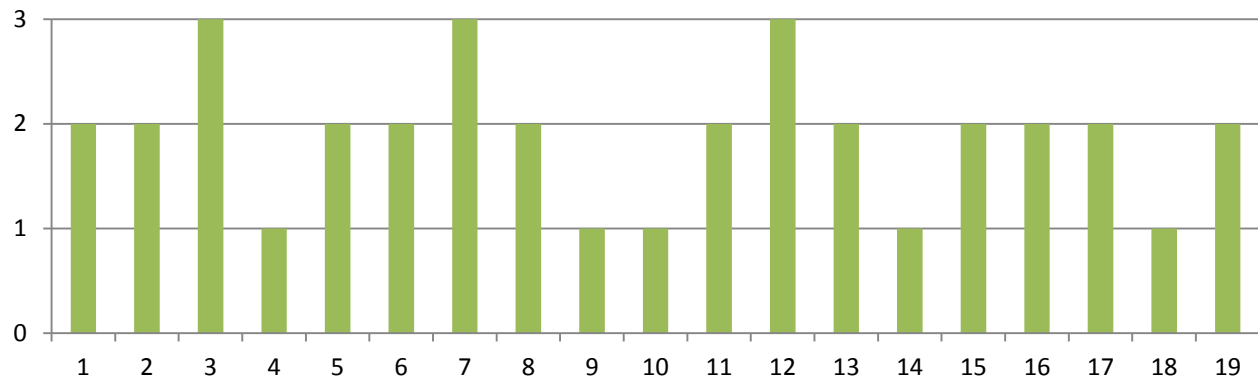


* 1. Sirturo; 2. Ferriprox; 3. Makena; 4. Promacta; 5. Exjade; 6. Levaquin; 7. Tysabri; 8. Luveris; 9. Fabrazyme; 10. Remodulin; 11. Cipro; 12. Celebrex; 13. Synercid; 14. Remicade; 15. Priftin; 16. Sulfamylon; 17. ProAmatine; 18. Biaxin; 19. Betaseron

The second key factor listed by FDA in its Draft Guidance is how well-understood the relationship is between the drug's effect on the surrogate or ICE and the disease process.⁸ Our study showed that, in several cases, there was only relatively weak support for the relationship between the surrogate and the disease process, such as in the case of Fabrazyme (where there was little evidence on the relationship between clearance of substrate in particular cell types and progressive deterioration of renal function). Again, a weaker showing in this particular factor was not a bar to Accelerated Approval, so here too FDA exhibited flexibility. Figure 2, below, illustrates the strength of the understanding of the relationship between the drug's effect on surrogate and the disease for each of the 19 drugs.

⁸ *Id.* at p. 19, lines 653-675.

Figure 2: Understanding of the Relationship between the Drug’s Effect on Surrogate and the Disease (0-3)*



* 1. Sirturo; 2. Feriprox; 3. Makena; 4. Promacta; 5. Exjade; 6. Levaquin; 7. Tysabri; 8. Luveris; 9. Fabrazyme; 10. Remodulin; 11. Cipro; 12. Celebrex; 13. Synercid; 14. Remicade; 15. Priftin; 16. Sulfamylon; 17. ProAmatine; 18. Biaxin; 19. Betaseron

In its Draft Guidance, FDA noted the critical role of the clinical strength of evidence of the drug both on the surrogate or ICE and on the clinical benefit as well, and our analysis below breaks this into these two separate sub-analyses. While FDA was not able to articulate generalizable principles with respect to the strength of clinical evidence,⁹ the power of our analysis is that by looking at the specifics of each of the 19 precedents, our analysis was able to ascertain that which may otherwise not be discernible.

With regard to strength of clinical evidence on their surrogates or ICEs, even therapies such as Sulfamylon, which had very weak strength of clinical evidence on its endpoints, was judged by FDA as appropriately qualified for Accelerated Approval, carried mainly on the strength of the evidence on other factors.

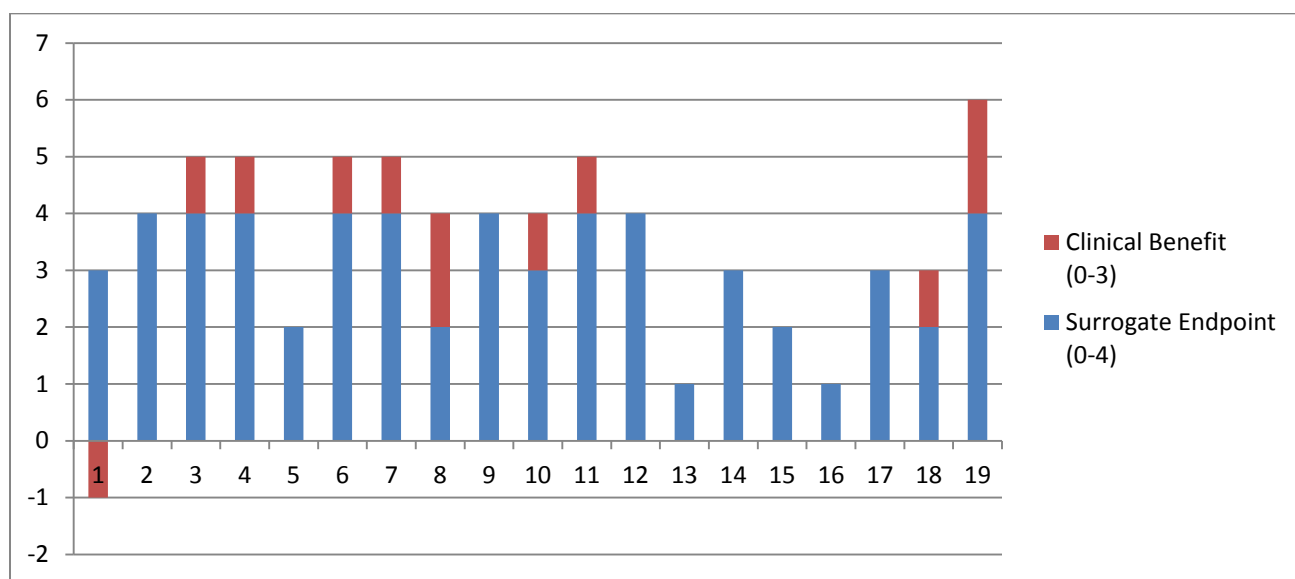
The second half of the assessment of overall clinical evidence was the strength of evidence of clinical benefit. It was not anticipated that these scores would be high for this factor, and generally the Accelerated Approval precedents had relatively little clinical evidence of

⁹ *Id.* at p. 18, lines 614-615.

benefit in the clinical data sets that were the basis for approval. Ten of the 19 precedents had essentially no substantial positive evidence of clinical benefit, and one of the precedents actually had a fairly strong negative numerical “lean” in clinical outcome evidence, suggesting that the therapy may have a negative impact on long-term clinical benefit.

Overall, our analysis shows that FDA was flexible in applying this third major factor to these Accelerated Approval precedents, just as FDA has with respect to the first two major factors. Figure 3, below, illustrates the strength of clinical evidence on both the surrogate/ICE and the clinical benefit for each of the 19 drugs.

Figure 3: Strength of Clinical Evidence (0-7)*



* 1. Sirturo; 2. Ferriprox; 3. Makena; 4. Promacta; 5. Exjade; 6. Levaquin; 7. Tysabri; 8. Luveris; 9. Fabrazyme; 10. Remodulin; 11. Cipro; 12. Celebrex; 13. Synercid; 14. Remicade; 15. Priftin; 16. Sulfamylon; 17. ProAmatine; 18. Biaxin; 19. Betaseron

As with my prior analysis of FDA’s orphan drug precedents,¹⁰ this analysis of FDA’s Accelerated Approval precedents testifies to FDA’s flexibility in applying this Accelerated

¹⁰ Frank Sasinowski, *Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs: Cataloging FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders*, 46 Drug Information Journal 238 (Mar. 2012) (Appendix 7).

Approval authority to therapies under FDA review. Robust compliance with all three major factors cited in FDA's Draft Guidance has not been required. Our analysis shows that FDA can exercise and has exercised substantial flexibility in applying the Accelerated Approval authority. Therefore, to embrace the mutual recommendations of PCAST and FDASIA for FDA to use this approval authority more will not require FDA to generate any new policies or procedures, nor will it require Congress to create and confer new authority, because it is my view that increased visibility and consideration of the Accelerated Approval pathway may achieve the desired result.

My proposal for achieving this increased visibility and consideration is a simple one: FDA could adopt a practice of considering whether each new therapy may be a candidate for Accelerated Approval. This could be considered at one or more of the key FDA/Sponsor interactions (that is, at the pre-IND, the End-of-Phase 2, the pre-NDA/BLA, and Advisory Committee meetings). Even though Sponsors have the option to request Fast Track designation, Sponsors and FDA have generally focused on traditional approval and therefore, Accelerated Approval has often not been considered. For instance, at two advisory committees I am familiar with (i.e., tolvaptan for autosomal dominant polycystic kidney disease in August 2013 and pirfenidone for idiopathic pulmonary fibrosis in March 2010),¹¹ the Accelerated Approval pathway was not discussed, even though both of these diseases are very serious and there were no therapies approved for either disease, and these considerations are the twin eligibility criteria for considering the Accelerated Approval pathway. In one way, my proposal is consistent with that part of the FDA Draft Guidance that encourages Sponsors who may be considering using an ICE in a program targeting Accelerated Approval to come in and discuss this approach with

¹¹ The publication of the results of a new trial on that day for this disease just were released on Sunday, May 18, 2014. King et al., *A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis*, N. Eng. J. Med., NEJM.org DOI: 10.1056/NEJNMoa1402582 (May 18, 2014) (Appendix 3).

FDA very early in the clinical development program.¹² Importantly, adoption of this proposal would not require enactment of any new statutory authority, nor would it impose anything more than a de minimis review of the potential qualification of each therapy for Accelerated Approval, that is, whether the disease being addressed is serious, and, if it is serious, then whether there already exists available therapy for that disease. Both of these are usually not difficult to discern. So the actions necessary to enable this proposal to be implemented are not heavy for Congress, FDA or Sponsors, and yet, the potential for expanding the use of Accelerated Approval by this simple measure are palpable.

Proposal #2: Using ICE more may Increase the Number of Accelerated Approval therapies.

PCAST recommended that FDA consider using Intermediate Clinical Endpoints (ICE) more often for Accelerated Approvals. Alex Varond and my (see above) was based on the 3 major factors in FDA's June 2013 Draft Guidance. It is my view that 2 of these 3 major factors would be significantly reduced in the FDA's review process if FDA and sponsors shifted to use ICE instead of unvalidated surrogates. Therefore, my second proposal is for Congress to encourage FDA and Sponsors to use ICE more often which would, according to our analysis, help FDA by reducing the demands of FDA's review of therapies under Accelerated Approval, and this may yield greater numbers of therapies approved by this pathway.

Intermediate clinical endpoints (ICE) present a largely untapped opportunity for Accelerated Approval. As mentioned in PCAST and in the FDA Draft Guidance, the use of ICE for Accelerated Approvals has been limited.

When FDA approves a therapy under Accelerated Approval using ICE instead of an unvalidated surrogate, FDA reduces the criticality or significance of two of the three factors

¹² Draft Guidance at p. 17, lines 580-582.

FDA considers in its Accelerated Approval decisions: both the need to have a clear understanding of the disease as well as the need to establish the relationship between the Accelerated Approval endpoint and the disease.

FDA's February 18, 2014 Accelerated Approval of Northera, the most recent Accelerated Approval, provides a helpful example.¹³ Northera was approved for the treatment of "orthostatic dizziness, lightheadedness, or the 'feeling that you are about to black out' in adult patients." Northera was approved on trials that relied upon an ICE, specifically: a short term benefit or acute improvement on dizziness, which is the main symptom and disability of the disease. By relying upon this ICE for this approval, FDA could have greater confidence that the confirmatory Phase 4 study will likely be able to establish the durable or chronic continued benefit in the long term of that same symptom improvement that was shown in the acute setting and was the basis for this Accelerated Approval. Because the ICE in this case is the ultimate clinical benefit but merely in an acute setting, understanding of the disease process and understanding of the relationship between the drug's effect on the Accelerated Approval endpoint and the disease were less important in this case than in Accelerated Approval decisions that rely on an unvalidated surrogate as the endpoint. In other words, because the primary endpoint of short term dizziness (i.e., the ICE) is the same primary endpoint that will be tested in the confirmatory Phase 4 study but will need to be shown that this benefit is sustained in a chronic setting (i.e., the ultimate clinical benefit), the degree of regulatory uncertainty is reduced relative to an approval

¹³ In addition to Northera, other examples of Subpart H approvals on ICE include Tysabri (ICE: decrease in relapse rate over the course of one year, clinical benefit: decrease in relapse rate over two years), Makena (ICE: reduction in preterm birth defined as less than 37 weeks, clinical benefit: improvement of infant outcomes, including death), Remodulin (ICE: combined exercise/Borg score analysis, clinical benefit: time to first occurrence of death, hospitalization for complications of pulmonary hypertension, need for esprostenol, or other clear evidence of deterioration), and Remicade (ICE: Clinical response defined as a reduction from baseline in the Crohn's Disease Activity Index Score of at least 70 points at the 4-week evaluation, clinical benefit: maintaining a sustained clinical outcome in patients with moderately to severely active Crohn's disease).

based on an unvalidated surrogate, and therefore the amount of evidence needed for these two factors— of understanding the disease and understanding the relationship between the endpoint and the disease— is lessened.

FDA’s April 2003 approval of Fabrazyme for Fabry disease provides an illustrative counter-example. Fabrazyme was approved under Accelerated Approval but relying upon evidence of the drug’s effect on an unvalidated surrogate: reduction of an intracellular substrate accumulation in the vascular endothelium. In this case, the ultimate clinical benefit was progression of renal disease and other significant clinical events. Because reduction of substrate accumulation is not an ICE and is not closely related to the ultimate clinical benefit, FDA needed to exert considerable regulatory scientific scrutiny to carefully observe and understand the Fabry disease process, as well as additionally to understand the relationship between the drug’s effect on the surrogate endpoint and the disease. Thus, each of these two FDA-listed factors was given more weight, more significance in the approval of Fabrazyme with its surrogate endpoint than in the approval of Northera with its ICE.

Therefore, if Sponsors and FDA turned to ICE for Accelerated Approvals, the demands on the FDA review process and more importantly, on the FDA approval decisions would be reduced, and it may be that more therapies as a result may be approved.

Proposal #3: Untap the Potential of a Traditional Approval Authority Through Use of a Simple Chart.

PCAST recommended that FDA use more of its existing “traditional” approval authorities. These traditional authorities includes the single study with “confirmatory evidence” statutory standard which was created in 1997, but which has had only limited visibility and even lesser use. One way to achieve both my first proposal (above) and this PCAST recommendation

would be for FDA to adopt a chart that could be used at each FDA Drug Advisory Committee (see Appendix 1). The proposed chart, in an uncomplicated and clear way, would present and made available for consideration all of the FDA’s existing approval authorities, along with the 2 major types of therapies for which FDA has historically exercised flexibility.

In 1997, under section 115 of the FDA Modernization Act, or FDAMA, Congress created a new statutory standard of evidence for FDA to use in determining whether a new medicine helps a patient. This evidentiary basis is an alternative to the standard Congress created in 1962, which FDA has usually interpreted as a requirement that two studies each prove a drug benefits a patient statistically, at a level of proof that tells FDA that these results could not have happened by chance more frequently than 1 in 20 times (p value of <.05). The 1997 provision allows FDA to approve drugs based on “one adequate and well-controlled clinical trial with confirmatory evidence.”¹⁴ While the third recommendation in the PCAST report was to “expand the use in practice of FDA’s existing authorities for confirmatory evidence,” by the time the report was published this recommendation no longer addressed the need for implementation of the key phrase of the FDAMA 115 statute: “confirmatory evidence.” The need for implementation of the phrase “confirmatory evidence” remains. To date, FDA has not promulgated regulations or provided guidance to industry or FDA reviewers on how to use this approval pathway by defining this key phrase and how to determine when that standard has been met.

For instance, the May 1998 FDA guidance on “Providing Clinical Evidence of Effectiveness” sets out 9 different ways in which a drug may be approved based on a single study;¹⁵ however, in practice, industry, the investment community, academia, and the patient

¹⁴ Section 115 of Food and Drug Administration Modernization Act of 1997 amending section 505(d) of the Federal Food, Drug, and Cosmetic Act [hereinafter FDAMA 115].

¹⁵ Food and Drug Administration, Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 8-12 (May 1998) [hereinafter May 1998 Guidance].

community, as well as often the FDA too, only recognizes the 9th of these 9 ways set forth by FDA. More importantly, this 9th means of proving effectiveness with a single study in FDA's May 1998 guidance is limited in the extreme. It is only applicable in very limited circumstances. For instance, this specific single study standard from the May 1998 guidance applies generally only when there exists a "statistically very persuasive finding [that is]... a very low p-value"¹⁶ and where to conduct a "second trial would be practically or ethically impossible."¹⁷

The FDAMA 115 alternative "confirmatory evidence" pathway created by Congress has not found meaningful foothold in the regulatory armamentarium. Only in a handful of occasions has FDA approved drugs with explicit reliance upon this standard. Let me review several of these so that you can see just how different the "confirmatory evidence" was with each case.

In 2004, FDA's Dr. Robert Temple, then Director of the Office of Drug Evaluation 1, approved, under FDAMA 115, the new drug Ventavis. In this case, the confirmatory evidence was the FDA's prior approval of two other "closely related" prostacyclin analogues despite those two other drugs being delivered by injectable means and Ventavis being inhaled.¹⁸ Further, Dr. Temple in that approval of Ventavis, noted that FDA had relied upon evidence of effectiveness from other drugs in the same class to approve new molecular entities. Dr. Temple specifically cited to the approval of Angiotensin II blockers for delaying renal function deterioration in Type 2 diabetes patients and to the approval of ACE inhibitors for treating congestive heart failure in which each approval relied on "single studies with p-values between 0.05 and 0.01 with the backgroup of multiple drugs in the class showing favorable effect."¹⁹

¹⁶ May 1998 Guidance, 13.

¹⁷ *Id.* at 15.

¹⁸ Memorandum re Iloprost, NDA 21-779, Cotherix, Inc. from Robert Temple, Director, Office of Drug Evaluation I, CDER, FDA (Dec. 27, 2004) (Appendix 4).

¹⁹ *Id.*

In 2008, FDA approved Banzel based on a single trial in patients with a specific seizure disorder, Lennox-Gastaut Syndrome (LGS), with the “confirmatory evidence” coming from 2 trials in a related condition, “partial seizures.”²⁰ The Sponsor had asked for approval for both uses, LGS and partial seizures, and while FDA judged the 2 partial seizure trials to be sufficient as confirmatory evidence of Branzel’s anticonvulsant activity to constitute the “confirmatory evidence” of Branzel’s benefit in LGS, FDA never approved Banzel for partial seizures. Dr. Temple approved Banzel and Dr. Rusty Katz, then the Director of the FDA Division of Neurology Products, stated at a public meeting that the evidence of effectiveness was established under the single study in LGS with the “confirmatory evidence” from the partial seizure studies, specifically as allowed by FDAMA 115.

FDA approved Xenazine in 2008 for the treatment of Huntington’s chorea based on a single trial with robust results on the primary endpoint, and a second trial that did not achieve statistical significance.²¹ FDA overlooked the lack of statistical significance in this second study because FDA judged that the estimate of the magnitude of the treatment benefit in the second study was identical to that seen in the single positive study. In the March 2006 “approvable letter,” Dr. Temple cited FDAMA 115 as the authority for such an approval.²²

There is room to build upon the wisdom in the May 1998 guidance so that drug developers, patients, sponsors, and FDA reviewers are aware of all evidence that may establish a product’s efficacy. There is the opportunity to better recognize and use the existing FDAMA 115 authority. For instance, I know of a drug in development for a rare disorder that has a Phase

²⁰ Banzel Summary Review, NDA 21-911, from Russell Katz, Director, Division of Neurology Products, CDER, FDA (Nov. 13, 2008), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021911s000_SumR.pdf.

²¹ Approvable Letter from Robert Temple, Office Director, Office of Drug Evaluation I, CDER, FDA, to Benjamin Lewis, Senior Director, Regulatory Affairs, Prestwick Pharmaceuticals, Inc. (Mar. 24, 2006), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021894s000_Approvable.pdf. (Appendix 5).

²² *Id.*

2 study indicating efficacy for treating the hallmark symptom of that disease, with another Phase 2 study in a related condition that report a statistically significant effect in a relevant symptom of that disease. If a single Phase 3 study is conducted in this rare disease population which achieves a p-value of less than 0.05, it may be that the results of the two Phase 2 studies could be sufficient to satisfy the “confirmatory evidence” standard of FDAMA 115.

Where there is scientifically-derived effectiveness information from any of a wide range of relevant sources in a new drug development program, this information should be considered. In the published report from a workshop on FDAMA115 and confirmatory evidence, the key author, Dr. Carl Peck²³ cites Dr. Janet Woodcock who presented the example at the workshop that, if a Sponsor were to seek to obtain FDA approval for an estrogen that was a new chemical entity for the prevention of osteoporosis, the Sponsor would only need to demonstrate improvement in bone mineral density in a single clinical trial.²⁴ Other substantial evidence supporting the lowest effective dose may still be needed to minimize toxicity, and evidence of dosing could come from the bone density trial or from a phase 2 dose-ranging trial.²⁵ Most importantly, Dr. Woodcock said that “additional studies would not be required because of extensive scientific understanding and acceptance of estrogen’s pharmacological effects on bone mineral density as a surrogate endpoint for osteoporotic fracture rate.”²⁶ In this example, class effects of estrogen on this use would constitute “confirmatory evidence” under FDAMA 115.

Clinical trial designs are no longer marked by nonspecific endpoints, inadequate blinding, unclear rules on analysis, and sketchy protocols. Second, replicate well-controlled trials to rule out unidentified biases in study design are therefore no longer needed in every case. In the case

²³ Dr. Peck had, at that time, recently been succeeded as Director of the FDA Drug Center by Dr. Woodcock.
²⁴ Carl Peck & Jill Wechsler, 36 *Drug Information Journal* 517, 526 (2002) [hereinafter Peck Paper] (Appendix 6).

²⁵ Peck Paper 526.

²⁶ Peck Paper 526.

of FDAMA 115, Congress has already given FDA the explicit authority, so now Congress could ask FDA to expand its exercise of this authority.

One way for Congress to support more fully FDA's embrace of this evidentiary basis to support a drug's approval, as well as to suggest a way for FDA to give exception to FDA's historic exercise of reasonable flexibility in regulating new inclusions would be for Congress to ask FDA to consider adopting a chart such as the one I am displaying (see Appendix 1) that could be provided to FDA reviewers or members of Advisory Committees to help them visualize the standards for statutory evidence of effectiveness, as well as the two types of therapies which FDA has demonstrated flexibility. As you can see from the first three rows, there generally are three ways to establish "substantial evidence of effectiveness" of a new therapy: (1) two adequate and well-controlled studies,²⁷ (2) one adequate and well-controlled clinical trial with confirmatory evidence,²⁸ and (3) a single study of providing highly persuasive and statistical evidence of an important clinical benefit, and where a confirmatory study would be difficult to conduct on practical or ethical grounds.²⁹ Then, as you can see in the final two rows, there are two classes of therapies for which FDA has historically exercised reasonable flexibility with respect to the quantum and quality of efficacy evidence required for approval: (1) Accelerated Approval Therapies and (2) orphan drugs.³⁰ The proposed chart, in an uncomplicated and clear way, would present and make available for consideration all of the FDA's existing authorities, along with two major types of therapies for which FDA has historically exercised flexibility.

Proposal #4: Issue a Guidance to Reduce Uncertainty and Communicate an Innovative Advance.

²⁷ 21 U.S.C. § 355(d)(7).

²⁸ FDAMA 115.

²⁹ May 1998 Guidance at pp 12-16.

³⁰ See Frank Sasinowski, *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloging FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders*, 46 Drug Information Journal 238 (Mar. 2012) (Appendix 7).

PCAST recommended that FDA increase its use of Guidances and White Papers to communicate innovative advances in regulatory science.³¹ FDA could be encouraged to issue a Guidance on the use of cumulative distribution analyses of clinical trial results as one way to aid in assessing the clinical meaningfulness of a therapy. FDA has been increasingly employing this type of analysis, and issuing an FDA Guidance or White Paper would give this type of analysis a broader and formal FDA endorsement, and this Guidance then would benefit drug development by clarifying the drug development pathway and by reducing regulatory uncertainty.

FDA ought to be and has been appropriately sensitive to refraining from imposing new regulatory requirements that are not explicitly in the statute. With respect to “clinical meaningfulness,” the statute requires sponsors to establish evidence that “the drug will have the effect it purports.”³²

The first time I heard an FDA official question whether a statistically significant study finding was also “clinically meaningful” to a patient was Dr. Robert Temple at an April 2006 advisory committee for a treatment of pain from anal fissures.³³ In the study of this therapy, pain was reported on a 100mm visual analog scale (VAS), and the drug-treated arm of the study showed a 29-point improvement from baseline, while subjects on placebo reported a 26-point improvement. There was some discussion during the committee’s proceedings about whether this numerical difference was a statistically significant difference. Dr. Temple instead conceded as a “thought-exercise” that this numerical difference was not due to chance but was caused by the drug, and then Dr. Temple asked, however, whether a patient suffering from anal fissure pain could tell the difference between a 29-point and a 26-point improvement between the average

³¹ PCAST Report at pp. 42-48 and PCAST Recommendation #1 at p. 54, item (iii).

³² FDC Act § 505(d).

³³ April 26, 2006 Advisory Committee on Cillegesie (nitroglycerin ointment).

patient's baseline pain score and that patient's pain scored at final visit. This was my introduction to the concept of "clinical meaningfulness," and FDA seemed to be articulating a very reasonable question. However, since that day long ago, some at FDA have taken the concept and challenged sponsors to establish by empirical evidence the "minimally clinically important difference" (MCID) for a study's endpoint prior to beginning the sponsor's pivotal clinical trial or trials. Not only does this impose a tremendous burden in terms of both time and resources which discourages and impedes innovation, but its utility is of uncertain value and may even be overtly misleading. Said more plainly, requiring this may not only deter and definitively delay development, but that deterrence and delay may be a price paid for achieving an MCID that may be of negative value.

In addition, any requirement to establish an MCID *a priori* and then analyze the results by only assessing "responders" generates waste in clinical trials, for we are then essentially ignoring all the subjects that happen to "fall short" of the MCID cut-point. More importantly, these MCID cut-points do not account for the heterogeneity in how each individual may differently assess "clinical meaningfulness" for that subject. In other words, these MCID cut-points are actually artificial, or population-derived values, that may not be relevant to individual patients. To understand this, consider the following example of FDA's February 2014 approval of Northera for orthostatic hypotension (OH). The key life-altering symptom for patients with OH is dizziness. When studying the effect of the drug Northera on dizziness, an MCID cut-point could have been established such that only those patients that reported an improvement of at least one point on the 11-point dizziness scale would be considered responders.³⁴ By doing so, all of the results on those subjects who reported an improvement of less than one point would be

³⁴ Northera (droxidopa) Label (2014), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203202lbl.pdf.

thrown out of the analysis, and ignoring study results is not sound statistically. In addition, for any subject, a 1-point improvement or above may not be the right definition for that person of “clinically meaningfulness.” Consider the hypothetical cases of a ballet dancer and a lawyer: two tenths of a one-point improvement might be meaningful to a ballet dancer if even that small amount of improvement enables that person to continue to dance, while conversely a lawyer with OH who primarily sits in front of a computer all day may need a two-point improvement for that to be of sufficient magnitude for it to be a clinically meaningful difference to that person.

In addition, when a drug company is required to select an MCID before conducting a trial, they are burdened with doing preliminary work to select the cut-point. They then also need larger and/or longer trials to detect a difference between drug and placebo/control arms in the study because the MCID responder analysis statistically is less sensitive to detecting between-group differences than a continuous variable.

As an alternative to MCID, FDA has been employing a “cumulative distribution” analysis of results, where a wide swath of different cut-points are analyzed. Cumulative distribution will improve interpretation of clinical trial data, as they show the full pattern of response using all subjects and results, and therefore, this type of analysis enables the entire distribution of responses to be compared between study groups. This is not a new concept for FDA for FDA has pioneered it and has reported such analysis in the labeling of several approved therapies. See below for excerpts from the labeling of the February 2014 approval of Northera for neurogenic orthostatic hypotension and the October 2013 approval of Adempas for pulmonary hypotension.

Table 1 - Nothera Cumulative Distribution Curve

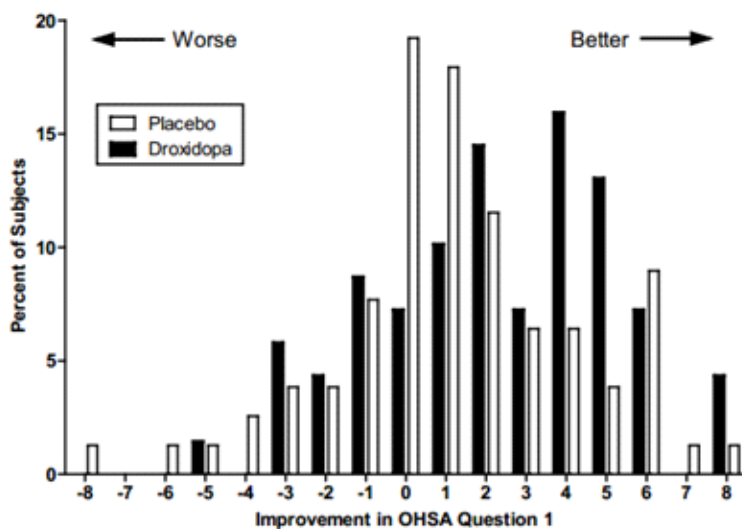
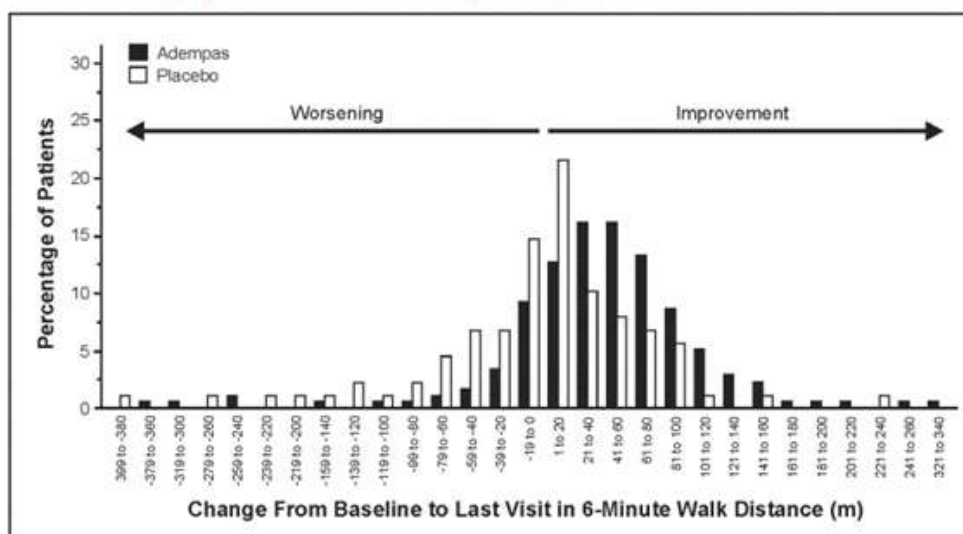


Table 2 - Adempas Cumulative Distribution Curve



Conclusions

1. My analysis of FDA's use of Accelerated Approval authority shows that FDA knows how to use this authority and indeed, how to use it flexibly. Therefore, to embrace the mutual recommendations of PCAST and FDASIA to employ this approval authority more will not require FDA to break new ground but to continue by expanding more what it has already done.

My first proposal is that this could be accomplished by adopting a practice of considering its Accelerated Approval authority for each new therapy.

2. Congress could recognize the historic flexibility FDA has exercised in its Accelerated Approvals (as well as in approving orphan drugs) and encourage further flexibility. Accelerated approval is not a rigid regime. It is necessarily flexible, and FDA has demonstrated its ability to act on therapies flexibly. To expand this flexibility, my second proposal is that Congress urge the increased acceptance and use of intermediate clinical endpoints (ICE).

3. Congress could also encourage FDA to expand the use in practice of its existing authorities for single-study approvals with confirmatory evidence under FDAMA 115, as was originally intended by Recommendation #3 in the PCAST report. As to my third proposal, as Appendix 1, I direct your attention to the chart, which is included in this written testimony, as a model for informing FDA reviewers, patients, sponsors, and Advisory Committee members about the options drug developers have to demonstrate a therapy's effectiveness, as well as to emphasize the two principle routes to FDA's historic exercise of flexibility in the case of both Accelerated Approval therapies and orphan drugs.

4. My fourth proposal is that Congress consider encouraging FDA to issue a Guidance on the emerging concept of "cumulative distribution" as a means of showing a therapy's clinical meaningfulness.

In these 4 ways, Congress could encourage the development and approval of treatments for serious and life-threatening diseases.

* * * * *

I thank you again for the invitation to participate in this hearing and hope these comments are valuable as you move forward with the 21st Century Cures initiative, and the Committee's work to accelerate the development of promising new treatments for patients.

Attachments

- Appendix 1: Proposed Advisory Committee Chart: Substantial Evidence of Effectiveness.
- Appendix 2: E-Filing on Regulations.Gov by Frank Sasinowski, Director, and Alexander Varond Hyman, Phelps & McNamara, P.C. re: Docket No. FDA-2013-D-0575, Comment on Section VII. C.: “Evidentiary Criteria for Accelerated Approval” of the FDA “Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics” (Aug. 26, 2013).
- Appendix 3: King et al., *A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis*, N. Eng. J. Med., NEJM.org DOI: 10.1056/NEJNMoa1402582 (May 18, 2014).
- Appendix 4: Memorandum re Iloprost, NDA 21-779, Cotherix, Inc. from Robert Temple, Director, Office of Drug Evaluation I, CDER, FDA (Dec. 27, 2004).
- Appendix 5: Approvable Letter from Robert Temple, Office Director, Office of Drug Evaluation I, CDER, FDA, to Benjamin Lewis, Senior Director, Regulatory Affairs, Prestwick Pharmaceuticals, Inc. (Mar. 24, 2006).
- Appendix 6: Carl Peck & Jill Wechsler, *Report of a Workshop on Confirmatory Evidence to Support a Single Clinical Trial as a Basis for New Drug Approval*, 36 Drug Information Journal 517 (2002).
- Appendix 7: Frank Sasinowski, *Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs: Cataloging FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders*, 46 Drug Information Journal 238 (Mar. 2012).

Appendix 1: Proposed Advisory Committee Chart

Substantial Evidence of Effectiveness		
Quantum of Effectiveness Evidence Needed		Source of Authority
1	Two Adequate and Well-Controlled Studies	21 U.S.C. § 355(d) ¹
2	One Adequate and Well-Controlled Study with “Confirmatory Evidence”	21 U.S.C. § 355(d) as amended by FDAMA 115 ²
3	One Study Providing Statistically Very Persuasive Evidence and Where a Second Study Would be Difficult to Conduct on Practical or Ethical Grounds	May 1998 Guidance ³
Types of Therapies in which FDA Has Exercised Flexibility		
A	Accelerated Approval/Subpart H/Fast Track Therapies	Historical FDA Precedents ⁴
B	Orphan Drug Therapies	Historical FDA Precedents ⁵

1. Federal Food, Drug, and Cosmetic (FDC) Act § 505(d)
2. FDA Modernization Act § 115
3. FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)
4. FDC Act § 506
5. FDC Act § 526

Frank Sasinowski's May 20, 2014 Testimony Before House E&C Health Subcommittee

On behalf of his law firm, Hyman, Phelps & McNamara, P.C., and as a Director of the National Organization for Rare Disorders (NORD), Frank Sasinowski offered the following.

1. Increase Accelerated Approval's Visibility and Use by Considering it for Each New Therapy.

Both PCAST and FDASIA recommended that FDA expand, beyond cancer and AIDS, use of its Accelerated Approval authority to approve medicines for those with serious diseases and no available therapies. Mr. Sasinowski's September 2013 analysis of the 19 therapies approved since 1992 (when FDA created Subpart H) shows that FDA has already been exercising considerable, reasonable flexibility in using this approval authority. This means that to implement the PCAST and FDASIA recommendation to use this authority more often, FDA would not need to establish any new program or policies, but may only need to give this approval pathway more visibility and more frequent consideration. Congress could encourage FDA to adopt a practice of considering whether each therapy may be eligible for Accelerated Approval. This simple change would require nearly no resources or time, but could have a huge impact on Americans' access to medicines for serious diseases. Also, see Proposal #3 below.

2. Using ICE More May Increase the Number of Accelerated Approval Therapies.

PCAST recommended that FDA consider using Intermediate Clinical Endpoints (ICE) more often for Accelerated Approvals. Mr. Sasinowski's analysis (see above) was based on the 3 major factors in FDA's June 2013 Draft Guidance. Mr. Sasinowski concludes that 2 of these 3 major factors would be significantly reduced in the FDA's review process if FDA and sponsors shifted to use ICE instead of unvalidated surrogates. Therefore, Mr. Sasinowski proposes that using ICE more would, according to his analysis, help FDA by reducing the demands of FDA's review of therapies under Accelerated Approval, which may yield greater numbers of therapies approved by this pathway.

3. Untap the Potential of a Traditional Approval Authority through Use of a Simple Chart.

PCAST recommended that FDA use more of its existing "traditional" approval authorities. These traditional authorities includes the single study with "confirmatory evidence" statutory standard which was created in 1997, but which has had only limited visibility and even lesser use. One way to achieve both Mr. Sasinowski's first proposal (above) and this PCAST recommendation would be for FDA to adopt a chart that Mr. Sasinowski proposes be used at each FDA Drug Advisory Committee (attached). The proposed chart, in an uncomplicated & clear way would present and made available for consideration all of the FDA's existing approval authorities, along with the 2 major types of therapies for which FDA has historically exercised flexibility.

4. Issue a Guidance to Reduce Uncertainty & Communicate an Innovative Advance.

PCAST recommended that FDA increase its use of Guidances and White Papers to communicate innovative advances in regulatory science. Mr. Sasinowski proposes that FDA issue a guidance on the use of cumulative distribution analyses of clinical trial results as one way to aid in assessing the clinical meaningfulness of a therapy. FDA has been increasingly employing this type of analysis, and issuing an FDA Guidance or White Paper would give this type of analysis a broader and formal FDA endorsement, and this guidance then would benefit drug development by reducing regulatory uncertainty.