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What Does the Future Hold for Patient-Focused Drug Development?

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I. INTRODUCTION

As Congress continues debating legislation intended to accelerate development of therapies and biopharmaceutical industry energies focus increasingly on the next user fee package (PDUFA VI), significant attention has been directed at Patient-Focused Drug Development or PFDD.

PFDD is a term of art coined by the Food and Drug Administration (FDA) in 2012 to embrace a number of provisions in the FDA Safety and Innovation Act (FDASIA) and its accompanying performance metrics. A core component of PFDD has been a round of disease area meetings called for in the industry agreement to better understand the patient perspective on a specific disease and its treatment options.

But PFDD is also being viewed more broadly than this one series of meetings and is fast becoming a high-priority issue for patients eager to exert greater influence over how medical products are reviewed and, ultimately, approved. It is also of high importance to therapeutic developers who would stand to benefit from laws and policies that ultimately give greater weighting and value to the patient's perspective.

The potential impact and value of PFDD is perhaps greatest in rare disease therapeutic development. The nature of rare disease—small populations and clinical trials, conditions that are often not well-categorized or understood and, in many cases, certain fatality given profound unmet medical need—have produced a patient advocacy community that has been a driver of PFDD, particularly during FDASIA.

Today, many of these same stakeholders are among the most enthusiastic proponents of the 21st Century Cures Act (H.R. 6), that passed the House overwhelmingly in July 2015, 344 to 77,[1] and of a companion innovation package being developed in the Senate. The Cures bill contains a number of PFDD-focused or influenced provisions that enjoyed strong bipartisan backing.

While the Cures package would further refine and build out PFDD, stakeholders are not standing still waiting for final legislation. Rather, a number of organizations, particularly patient advocates, are moving forward to develop various products and to push for their validation and use by regulators and trial sponsors. FDA's recently issued *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment*,[2] informed heavily by a draft guidance produced by the Duchenne community under the leadership of Parent Project Muscular Dystrophy,[3] is a landmark example of how PFDD writ large is seeking to reshape the regulatory environment.

CORE RECOMMENDATIONS

- PFDD Developers and stakeholders should develop a comprehensive policy agenda to address current and emerging needs going in to PDUFA VI. This should build upon FDASIA provisions and any further gains achieved in 21st Century Cures and related packages and focus on core priorities and needs such as FDA guidance and structure in reviewing and validating PFDD tools, oversight of how such tools will ultimately be used, and costs to address these needs.
- PFDD developers and stakeholders need to engage as soon as possible with payers to obtain this important perspective and determine ways to engage payers in PFDD development.
- Patients and other parties interested in developing PFDD tools should proceed concurrent with legislative and regulatory engagement. As seen in some of the examples below, proactive patients are driving this agenda right now.

As the enthusiasm for PFDD continues on both Capitol Hill and among stakeholders, several important questions and challenges loom ahead, particularly as legislators, regulators and industry ramp up for the next round of user fees, PDUFA VI, due in just two years. While many have applauded PFDD as being long-overdue, skeptics and critics remain, particularly consumer interests who have expressed viewpoints that such provisions may lessen regulatory standards and increase patient risk. And beyond the area of medical product approval, the simmering debate about the cost of specialty drugs is raising questions as to how payers will react to products whose approval may have hinged upon a PFDD authority or tool.

Ultimately, what will the impact of PFDD be on regulatory review as well as coverage and access decisions?

This article will explore the history and fundamentals of PFDD from FDASIA to 21st Century Cures and on to PDUFA VI. It also examines the challenges and opportunities stakeholders will need to factor in creating these regulatory tools and in developing the PFDD agenda for the future.

II. MEANINGFUL PATIENT ENGAGEMENT & LEADERSHIP

Patient advocacy organizations—and their industry and other allies—have long been influential voices in shaping health policy laws. Annual advocacy days or "fly-ins" consisting of patients and their caregivers are commonplace, and most lawmakers make time to visit, even if briefly, with these constituents and their compelling stories.

For many of these organizations, their policy agendas over the past two decades focused primarily on two main buckets:

1. Increasing funding for medical research supported by the National Institutes of Health (NIH), including resources targeted as best possible to research on specific diseases or conditions; and

2. Building public health programs through the Centers for Disease Control and Prevention (CDC) such as prevention initiatives and disease surveillance, registries, and other data gathering projects.

In terms of FDA, the aggressive tactics employed by HIV/AIDS activists in the late 1980s are well-known and are seen by many as being pivotal to increasing government attention and action to the AIDS crisis.[4] But beyond the HIV/AIDS movement, most other patient-led or co-led advocacy efforts have focused largely on securing increased funding to support the work of the agency. The Coalition for a Stronger FDA and its predecessor organizations, a collaboration of numerous patient organizations as well as industry, has historically led this effort.[5]

But in recent years, as the research and public health labors in many areas began to bear fruit in terms of potential therapies, patient advocates have been devoting more time and energy toward FDA regulatory issues beyond funding. Some examples of these efforts include the Unlocking Lifesaving Treatments for Rare Diseases or ULTRA Act, first introduced in late 2011 and the follow-on Faster Access to Specialized Treatments or FAST Act, introduced in 2012. The bills were sponsored by former Reps. Cliff Stearns (R-FL) and Edolphus Towns (D-NY) and were embraced by many rare disease advocates, including the Everylife Foundation.[6] At their core, these regulatory reforms aimed to drive increased use of the Fast Track and other expedited pathways for rare disease therapies, and the concept was ultimately reflected within FDASIA.

FDASIA also included several other policies championed by patient advocates. These included provisions to expand FDA's use of external experts, including the patient, within the medical product review process, to create another expedited pathway known as Breakthrough Therapies for treatments demonstrating early clinical superiority over existing treatments and to establish an incentive to develop treatments for pediatric rare diseases by providing developers with a Priority Review voucher they could use on other applications or could sell.[7] Beyond statutory provisions of FDASIA, the corresponding FDA/industry agreement contains numerous goals and performance metrics focused on rare disease therapy development, a further sign of the influence patients and related stakeholders had in the overall process and in industry's interests in PFDD opportunities. These include increasing staff, enhancing reviewer education and training on relevant topics, issuing guidances pertaining to rare disease therapy development and convening 20 meetings over the five-year performance window to gather patient perspectives and views on benefit/risk and related issues associated with specific diseases or conditions.[8]

III. FROM FDASIA TO 21ST CENTURY CURES

A great deal of activity has unfolded during the three-plus years since FDASIA was enacted to continue building momentum toward patient-focused drug development. In May 2014, FDA issued its final guidance on usage of its expedited approval tools. The draft guidance, issued the previous June, was criticized by several rare disease advocacy groups and members of Congress who maintained that the guidance did not go far enough in providing specific directions to address applications for rare patient populations.[9]

FDA has also convened several PFDD disease area meetings, as noted above. In early July, FDA released the final eight disease area topics selected for meetings over the coming two years to round out the provision of the user fee agreement.[10] Some stakeholders have questioned how the conditions were selected and what, ultimately, will be the impact of the meetings on agency decision-making.

Most recently, in mid-September 2015, FDA announced that it would establish a Patient Engagement Advisory Committee to advise the agency on where, when, and how the patient can provide input on product development and how the agency should work with patients on such issues. The announcement package included solicitations for nominees to the panel.[11] This action further demonstrates the weight the agency is giving to patient-engagement issues and elevates the standing of patient advisors at the agency.

Beyond these agency-driven actions to implement FDASIA, some of the most impressive actions have been generated by an empowered and sophisticated patient advocacy community; individuals and organizations who are unwilling to sit and wait for the agency are proactively bringing attention to their specific disease or condition.

The Duchenne muscular dystrophy advocacy exemplifies this proactive approach. An enthusiastic backer of the FDASIA reform provisions, the Parent Project Muscular Dystrophy (PPMD) organization would in the year following FDASIA embark upon an effort to deliver to FDA a scientifically rigorous quantitative perspective on the benefit/risk threshold from nearly 120 parents and guardians of boys and adolescents with Duchene, a form of the disease that is typically fatal by the late 20s. The survey, developed by the organization in partnership with experts at Johns Hopkins University, sought to deliver actionable evidence beyond patient anecdotes to inform FDA review of the first ever new drug applications for this underserved population.[12]

Following the benefit/risk survey, PPMD mounted a year-long process to create a landmark, patient-driven drug development guidance for FDA and sponsors. This initiative came to involve dozens of experts with academic, clinical, and industry backgrounds focused on core topics for accelerating the development and regulatory processes. This externally-prepared draft guidance was delivered to FDA in June 2014. Following a public comment period in the fall of that year, in June 2015, FDA issued a draft guidance of its own, deeply informed by the community's collaborative efforts.[13] A 60-day comment period closed in early August.

Both the benefit/risk survey and the patient-driven guidance drew widespread praise from FDA, congressional leaders, and the rare disease community. "The U.S. Food and Drug Administration is appreciative of the input of Duchenne patients and patient advocates. Their input will enhance the essential data-driven process and evaluation of new therapies," said Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research.[14] The guidance's timing may be quite fortuitous, with three pending applications before the agency and a looming pre-Thanksgiving two-day Advisory Committee meeting focused on two of the candidate therapies.[15]

Amid the intense interest in the Duchenne-related initiatives, advocates for other conditions have taken their own similar steps forward. Alzheimer's stakeholders, for example, are embarking on a public-private partnership to build a global clinical trials network and patient registry platform, an effort that includes FDA and NIH.[16] This work seeks to address the sluggish pace of patient enrollment in Alzheimer's clinical trials as the dominant theory suggests the trials need to start much earlier in the disease process when symptoms may be barely visible. And one year after the Ice Bucket Challenge phenomenon, the ALS community has launched its own drug development guidance and clinical trials guidelines projects[17] that implement priorities earlier identified in a 2013 FDA Part 13 meeting on the disease.

A. Congress Acts…Again

As FDA and patient advocacy groups move ahead, lawmakers in Congress are not standing by idly. Over the past 18 months, many influential legislators have labored to advance an ambitious piece of legislation focused on reducing the time and resource burden typically needed to develop new therapies. Dubbed the 21st Century Cures initiative and launched in spring 2014 by Energy & Commerce Committee Chairman Fred Upton (R-MI) and senior Democrat Diana DeGette (D-CO),[18] the effort has drawn accolades from much of the patient advocacy community. It passed the House by a wide margin in early July, but its fate remains uncertain. Senate lawmakers are interested in many similar issues and are working on their own draft bill, but the process is at an earlier stage of development in the upper chamber and notable policy differences exist between the two chambers. Senate leaders on the legislation are hopeful that draft legislation will be issued in late summer or early fall and that the Health, Education, Labor and Pensions (HELP) Committee will act on the bill by the end of 2015 with final Senate action occurring in early 2016.

The 21st Century Cures bill is unique for several reasons. It encompasses a broad swath of the research and development continuum including both FDA regulatory topics and the earlier research stage led by NIH. Additionally, if enacted in its current form, the bill would take action on FDA issues more typically addressed in the five-year user fee cycle. Chairman Upton, who is completing his final two-year term as Chairman of the Committee under Republican Conference rules, sees the 21st Century Cures bill as a capstone of his committee work that needs to be enacted by late this year or early 2016 before Washington's attention shifts increasingly to the national elections. Absent such action, the likelihood that the measure fails to be considered as part of PDUFA VI increases markedly.

In many ways, the journey of 21st Century Cures has been a compressed version of the ups and downs common in medical product research and development itself. The second half of 2014 featured a number of hearings, panels, and regional forums in which diverse stakeholders lauded the effort as they presented their ideas for inclusion. Amid a highly partisan and divided Congress gridlocked during a mid-term election, 21st Century Cures stood out as a bright spot in a largely barren legislative landscape. But the initial draft bill was panned by many Democrats when released in January 2015, and Upton and colleagues had to work for several months to revive the bipartisan approach, achieved in no small part by adding a guaranteed funding stream for NIH research and by cutting back on development incentives criticized by consumer advocacy and other interests.[19]

While the path ahead for 21st Century Cures remains fraught with challenges, the good news for patients and other champions of PFDD is that the topic enjoys a strong and expanding level of bipartisan support. For example, this past June, at the urging of the Duchenne community and supported by a coalition of more than 50 stakeholders, a bipartisan group of Senators introduced legislation known the Patient-Focused Impact Assessment Act or PFIA (S. 1597).[20] This bill recognizes the push toward more widespread development and use of PFDD strategies by calling for FDA to develop a publicly accessible checklist of how reviewers did—or did not—use PFDD tools (e.g., patient-led benefit/risk studies, patient-reported outcomes, etc.) in making regulatory decisions. The goal of the sponsors and supporters is to use the publicly-disclosed assessment to encourage further investment and innovation in the science behind these innovative tools.

Given the legislative momentum behind PFDD, the depth of support among the patient stakeholder community and the increasing level of interest among industry, the field seems well-positioned for further gains, particularly as attention turns to PDUFA VI.

IV. PFDD IN PDUFA VI AND BEYOND

While 21st Century Cures moves forward, overlapping timelines demand that stakeholders look to the future and, to paraphrase hockey legend Wayne Gretzky, focus on where the policy is going or needs to be going rather than where it is today. A number of forward-looking areas are described below where more opportunity exists for the PFDD agenda.

A. Greater Clarity & Definition to PFDD Regulatory Process

As a nascent field, patient-focused drug development tools are emerging with a relatively skimpy regulatory framework. In some ways, this could be an advantage. Reams of guidance and regulation can become an undesired wet blanket that smothers innovation. At the same time, a certain level of direction and guidance may be needed to focus energy and resources on PFDD products that, in the end, achieve the goal of improved regulatory performance in all directions.

As the Duchenne community found over the past year, the agency was building the plane while flying it and needed to establish the process to receive and solicit public input on the community-generated guidance, an action that likely added precious time to the overall process. Although understandable at this early stage of PFDD, refinement and definition of the overarching process—as well as the avoidance of unnecessary burdens—should be a top priority of stakeholders.

21st Century Cures moves in this direction with provisions that would institute a process for submission and review of patient experience data and a detailed process for reviewing and qualifying biomarkers and other drug development tools (Sec.2021).[21] But these provisions do not address the entirety of PFDD, nor do they establish standards for review and validation of these and other tools. Ultimately, PFDD developers and users will need to determine the level of specificity they believe is necessary and attainable and pursue this going forward.

B. Funding PFDD

In addition to continued ambiguity and gaps in the PFDD process, another lingering question is how FDA will resource the agency's work reviewing and validating what would hopefully be an influx of PFDD tools, begging the question of whether PFDD developers should support at least part of this work. One approach could be to fund the enhanced activity through the annual FDA appropriations process. But the reality of constrained federal budgets for the foreseeable future clouds the likelihood of full funding from the government, at least any time soon.

An alternative approach could be a public/private partnership model. For more than 20 years now, industry has helped fund the work of FDA through user fees in exchange for commitments to more timely reviews and corresponding performance measures. Would a similar approach be viable for PFDD tools? While potentially controversial to some who may balk at the added costs, a partnership approach would demonstrate a shared commitment to use the tools and may be more palatable to legislators concerned about government spending. On the flip side, it also could raise numerous questions and concerns around who pays the bill and the benefits associated with such costs. If patient stakeholders continue to drive PFDD development, adding regulatory review costs to the tab may dampen such interest. Conversely, were industry to cover such costs, could this produce a conflict if the tool is used to inform review of that same company's application?

Should stakeholders choose to put forward a PFDD user fee or other funding proposal, it would be important to consider the primary goals of the initiative. These may include:

- Review times and other performance metrics modeled on timelines included in user fee packages;
- Detailed processes for the submission, review, refinement and, ultimately, approval or validation of PFDD tools;
- A process by which the agency will report annually on its record in receiving, reviewing and validating PFDD tools and how such tools were used by reviewers; and
- A clear understanding of whether and how these validated tools would be publicly accessible.

Developing a comprehensive PFDD qualification pathway would not be simple. But if stakeholders expect PFDD to become a sustained component of the drug development landscape, it may be difficult to avoid this rigor.

V. DON'T FORGET THE PAYER

While patient, industry and regulatory collaboration in developing PFDD tools is emerging rapidly, stakeholders also should consider the merits of engaging payers, including the Centers for Medicare and Medicaid Services (CMS), in these conversations. Some may have a visceral reaction to this notion, but the ongoing and intensifying "access wars" with payers increasingly balking at covering costly, new therapies will likely intensify over the coming years as the innovative science comes to market. PFDD tools that enable the development process may be stymied from achieving their ultimate goal of changing patient outcomes if substantial barriers in reimbursed health markets are erected.

The cost of novel therapeutics has been a dominant health policy topic over the past eighteen months. Driven significantly by the approval of a transformative drug for treating hepatitis C, Sovaldi and follow-on products, this issue is central to patients, particularly those with unmet medical needs. The $300,000-plus annual wholesale price of the Cystic Fibrosis drug Kalydeco[22] and similar or greater six-figure charges for other novel therapies such as Soliris, which is used to treat a rare blood disorder, and Naglazyme, used to treat the rare disease mucopolysaccharidosis IV, may only be harbingers of what is to come.[23] Given this predictable collision between six-figure therapies for increasingly targeted therapies on one hand and payers and employers looking to better manage the total cost of care on the other, it seems clear that a new paradigm will be needed to reap the rewards of our nation's unique efforts to drive biomedical innovation into the clinic.

Over the past year, the payer and employer constituencies have fought back aggressively. In June, Avalere Health issued an AHIP-funded study indicating that 10 existing or anticipated drugs that received Breakthrough Therapy designation would add nearly $50 billion to federal healthcare costs over the next decade.[24] During the 21st Century Cures debate, AHIP was largely silent aside from opposing a proposed offset that would have reduced payments to Part D plans by between $5 billion to $7 billion. In addition to

AHIP, employers have been another voice raising concerns about the cost of drugs.[25] In 2014, the National Coalition on Health Care, whose organizations include corporations, unions, medical professional societies, and other advocates, launched the Campaign for Sustainable Rx Pricing to increase attention and visibility on the issue.[26]

A. Proactively Engage Payers

These examples make clear the extent of the challenges looming ahead for patients seeking access to novel but pricey therapies and underscore that regulatory clearance of a drug is not synonymous with access. If a costly therapy is approaching the market, patient advocates in particular should consider engaging with payers well before FDA approval. This is even more important if the product is being reviewed through an expedited pathway where the evidence of clinical benefit may be less robust than is produced through a traditional Phase III clinical trial.

To prepare for interaction, patient communities should consider assembling data to demonstrate both the clinical and cost impacts a new treatment will have on patients and, ultimately, the payers covering the bulk of their care. For example, the hepatitis community has been aggressive in promoting that the total value of drugs like Sovaldi outweighs their relatively high cost, since they are curative, have a limited course of treatment, and, in the most severe cases, can negate the need for liver transplants and other costly, late stage intervention. Making this case for the overall value of a new therapy will be more challenging in situations where the costly treatment addresses a chronic condition and will thus need to be taken for years or decades and where it may be disease-modifying rather than curative.

Patients and other PFDD stakeholders should obtain the payer perspective on PFDD as part of such engagement, ideally early enough in the process so this input could shape the overall product development. If a PFDD tool in question is a patient experience or preference instrument, payer perspectives on how this data may be received by those weighing reimbursement could be critical. Similarly, if stakeholders are considering alternative trial designs, payer perspective could provide an early indication of potential access challenges that could arise under certain regulatory approval scenarios.

Earlier this year, many stakeholders were pleased that FDA approved a device to treat obesity despite the trial falling short on its primary endpoint because the agency was influenced, at least in part, by the preferences of the patient population as quantified in a survey tool.[27] This marked the first time inputs of this nature clearly informed the agency's approval decision. While patient advocates and others should be encouraged by this influence of preference data in the regulatory process, the flip side would be potential for payers to conclude that such evidence was insufficient to show the therapeutic value they expect to see in coverage of new treatments and therapies. Engaging payers on PFDD does not guarantee a favorable coverage decision but could maximize the impact of the tool in reimbursement decision-making.

B. A Little Blue Sky Thinking

Even if payers are engaged early and fully in developing PFDD tools, the trend toward six-figure drug prices and push back seen so far suggests the issue will not vanish anytime soon. The big question, really, is whether or not workable solutions that recognize the high cost and risks of drug discovery and development without breaking the banks of payers, employers and individual consumers can be developed.

Just as PFDD has ushered in a more collaborative relationship between patients, industry, and regulators, perhaps we are at the threshold of an era of similar engagement between patients, industry, and payers. Simply put, is "Patient-Focused Benefit Design" in our future and what might this look like?

So far, a handful of thinkers have put forward innovative but still rough ideas to help manage six-figure annual drug costs. Dr. Scott Gottlieb of the American Enterprise Institute, who has held senior positions at FDA and the Centers for Medicare and Medicaid Services (CMS), has proposed amortizing the costs of such therapies over time similar to the way most people pay for home mortgages.[28] The mechanics of such a scheme would be complex, particularly if clinical milestones that trigger payments are added to the mix and presuming that, just like with mortgages, there will be a desire for some sort of backstop to protect against those who ultimately do not pay their bills. Other factors to consider include the duration and total cost of the therapy—a one-time cost of $100,000 vs. $100,000 or more each year would have very different total price tags—as well as the churn in the insurance market and if or how such a debt would move with a patient from payer to payer.

Another concept batted around is the application of a reinsurance mechanism to cover extraordinary drug costs similar to how reinsurance is used today to protect against catastrophic events. But with an increasing number of patients using or interested in using such treatments, it may be that even a model like this would be unsustainable without limiting access in other ways or coming up with a significantly altered approach to such an instrument.

Through Patient-Focused Benefit Design, patients and payers would need to engage in frank discussions as to what the patient wants and values in a benefits package. Just as PFDD contemplates higher levels of patient tolerance for potential risk in exchange for adequate benefits, it would be fair for PFBD to explore patient perspective on costs in exchange for access to novel therapies. For example, could we envision a situation where patients might, in exchange for more affordable access to a specific novel therapy, opt for higher out-of-pocket costs for other therapies or types of care? This kind of strategy could be particularly appealing if a therapy can be shown to avoid or limit the use of other expensive healthcare services.

VI. CONCLUSION

Patient-Focused Drug Development has come a long way in a relatively short period of time thanks in large part to a motivated and empowered patient community that is demanding access to novel treatments. The coming years will be a critical phase as this nascent field "grows up" and as aspirations for the next round of user fee agreements crystalize. Stakeholders have no time to waste in either bringing the patient perspective to the regulatory process and in developing a compelling value proposition for payers and the larger healthcare marketplace. Nothing short of a revolution is occurring as the patient advocacy community demands a meaningful role across the development pipeline and prepares itself to fundamentally alter the way in which a new therapy can reach the clinic. The returns on this investment could be staggering.

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FDLI's *Food and Drug Policy Forum* provides a marketplace for the exchange of policy ideas regarding food and drug law issues. The *Forum* welcomes articles on cutting-edge state, national, and international policy issues related to food and drug law.

FDLI's *Food and Drug Policy Forum* is designed to provide a venue for the presentation of information, analysis, and policy recommendations in the areas of food, drugs, animal drugs, biologics, cosmetics, diagnostics, dietary supplements, medical devices, and tobacco.

Each issue of the *Forum* presents an important policy topic, provides background information and detailed discussion of the issues involved in the policy question, relevant research, pertinent sources, and policy recommendations. This publication is digital-only, peer-reviewed, and smartphone enabled.

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