Testimony submitted to the Senate HELP Committee for the hearing
"Continuing America's Leadership: Advancing Research and Development for Patients"
March 24, 2015
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Chairman Alexander, Ranking Member Murray, and members of the committee. My name is Allan Coukell. I direct health programs at The Pew Charitable Trusts, an independent, non-partisan research and policy organization with a number of initiatives focused on drug and medical device safety and innovation.

Thank you for the opportunity to present testimony on the medical product development landscape. I will focus today on steps that could support innovation, with a particular emphasis on the need for robust clinical data to evaluate product performance both before and after approval. I will touch, in particular, on drug approvals and Pew's medical device and antibiotic innovation work, as well as on FDA predictability.

In addition to touching briefly on FDA operations, my testimony makes three key points:

- The rising cost of medical product innovation is a serious concern, with multiple underlying causes.
- The FDA has great flexibility, but would benefit from additional tools in some areas.
- The need for robust clinical data is higher than ever, and there are steps Congress could take to improve the efficiency of data collection.

Since 1950, the Food and Drug Administration (FDA) has approved more than 1,400 drugs. Aside from an increase in approvals after the enactment of the first Prescription Drug User Fee Act (PDUFA), the number of annual approvals has been relatively constant over this period,[1] while the inflation-adjusted cost of bringing these products to market has risen steadily. As numerous reviews and analyses have shown, the regulatory environment is not the sole, nor even the principal, cause of this declining productivity.[1-3]

Nevertheless, it is imperative that FDA regulation and other public programs that support innovation work as efficiently as possible. Patients, clinicians, and product developers rely on the FDA's careful and efficient review of new products.

Pharmaceutical research and development investment in the US has remained flat over the past decade, while investments in medical device and biotechnology, though much smaller, have grown steadily.[4] The United States continues to lead the world in many aspects of biomedical innovation,[4-6] and recent scientific and clinical advances are encouraging; however, there are

very real strains in the business models for both drug and medical device development – and in our ability to manage the associated costs of these products.

FDA approvals and flexibility

In approving new drugs, FDA relies on a "substantial evidence of effectiveness" standard established by "adequate and well-controlled investigations, including clinical investigations." The medical device standard is similar: "reasonable assurance of safety and effectiveness" based on "valid scientific evidence."

There is no "one size fits all" requirement for evidence to support drug or device approval. For example, an analysis by the National Organization for Rare Disorders found that of 135 drug approvals for non-cancer rare disease, 45 met traditional data requirements, 32 reflected "administrative flexibility" based on a previously documented FDA system, and 58 reflected flexibility applied on a case-by-case basis.[7] Another recent analysis of all drug approvals (funded by Pew) found that while FDA generally relied on randomized clinical trials to approve therapeutics, over one third of approvals were based on a single efficacy trial.[8] This same analysis also showed that FDA used flexibility with regards to which outcomes these trials had to measure.

FDA's review of safety and effectiveness data is essential to inform patients and physicians. For many drugs and devices, the clinical effects are difficult to distinguish from the normal variation in outcomes seen in the relevant population of patients. Often, a drug's effect can only be assessed across large numbers of patients through careful experiments designed to reduce confounding and accidental bias. The crucial point is that the size of clinical trials is driven, *not by the approval standard written in statute*, but by the difficulty of discerning the effect of the treatment.

It is important to note that early promise for drugs and devices may not be borne out as the products proceed through development. A recent Pew study found that even among medical devices that the FDA had identified as sufficiently innovative to qualify for priority review status, approximately one third were not ultimately approved.[9] This shows, again, that novelty and early promise are not always borne out by more thorough testing.

Several existing mechanisms provide flexibility for the data collected. The accelerated approval pathway for drugs, which Congress codified into law in 2012, allows FDA approval based on surrogate—rather than clinical—endpoints, with the goal of enabling more efficient premarket studies. In 2014, FDA approved 20 percent of novel new drugs through this pathway.[10]

Similarly, for devices that treat or diagnose conditions affecting fewer than 4,000 patients per year, FDA can grant a humanitarian device exemption, which allows the marketing of a product

that is considered safe and is expected to provide benefits, even if less evidence on effectiveness is available. The FDA's proposed expedited access premarket approval (EAP) process for medical devices would also support the marketing of new medical devices based on surrogate endpoints, shorter clinical trials or other adaptive designs. The success of this policy, though, relies on the efficient collection of data—both pre- and post-market. Congress should explore codifying this program in statute, and should address some gaps in FDA's authority to accelerate patient access to new medical devices while still collecting sufficient information throughout a product's entire life cycle. In particular, Congress should assess the agency's ability to promptly remove the approval of devices that ultimately were not found to be safe and effective.[11]

These programs provide FDA with significant latitude to tailor the data collected by sponsors and the agency's review process to reflect the severity of the disease and availability of alternative treatments, not to mention each product's risks and benefits.

Limited Population Antibacterial Drug approvals

One area where Congress could facilitate innovation is the development of a new regulatory pathway for FDA to approve new antibiotics for specific, limited populations of patients with life-threatening infections where few or no treatment options currently exist.[12] We have an urgent need for new antibiotics. Antibiotic resistance is rising and there are increasing infections for which we have almost no treatments. Currently, for the FDA to approve a new antibiotic the FDA generally requires extensive clinical trials in the larger population due to concerns about safety risks resulting from possible use in broader groups. It would be desirable to have a pathway—twice endorsed by the President's Council of Advisors on Science and Technology (PCAST)[13]—under which such drugs could rapidly reach high-need patients while reducing the risks from wider use of the drug. There would also be clear public health benefits to limiting the use of new antibiotics effective against drug-resistant bacteria, to stave off the emergence of drug-resistant strains.

Senators Hatch and Bennet have introduced the PATH Act, S.185, which would direct FDA to create this pathway for antibiotics. A number of key stakeholders, including public health groups, providers, industry, and venture capital, support this legislation, and we ask the committee to move this bill quickly.

Patients may need more evidence

It is important to note that current approval standards speak only to efficacy and safety. Stakeholders beyond the FDA – notably patients and payors – may frequently need additional information to make informed choices. For a patient, the question may not be whether a drug is effective compared with a placebo, but whether it is superior to other existing treatments. Patients and payors alike may seek to evaluate that information and weigh it against the drug's cost. These are crucial questions for the individual that are not addressed by the current approval

standard. In addition, drug costs – particularly for high-cost biologics that make up an increasing share of drug approvals – are rising faster than healthcare costs as a whole. The need to sustainably mange health-care spending is likely to drive further demands for data to assess the value of new drugs and treatments, and not merely their effectiveness.[14] For example, one of the nation's leading cancer centers recently announced that it would not utilize a particular new cancer drug because the drug was more expensive than its competitors, but did not confer additional benefit.[15]

Better data at lower cost

To facilitate more efficient collection of evidence in both the pre-market and post-market setting, it is important to address the rising cost of clinical trials and clinical data acquisition. Clinical trials remain the most reliable source of unbiased information for evaluating clinical effectiveness,[16] and Congress could help address these costs by facilitating faster trial initiation through, for example, greater use of central institutional review boards (IRBs) instead of multiple local reviews. For medical devices in particular, trials are currently required by statute to obtain IRB review at each facility participating in a study.[17] Removing this requirement could help streamline the approval of these trials.

Personalized, or precision, medicine has the potential to identify sub-populations of patients with specific genetic profiles who are more likely to respond to a particular therapy – particularly in cancer treatment. To take full advantage of this potential will require innovative trial designs, which the FDA has encouraged. For example, the recently developed Lung-MAP trial has the potential to improve efficiency by allowing simultaneous and sequential comparisons of multiple drugs (from multiple companies) and stratification of patients by genotype.[18]

Per patient costs and large simple trials

Independent of the size of the trial, per-patient clinical trial costs have risen sharply. A 2013 survey found that phase III costs rose by 86 to 88 percent over three years (from $25,000 to $40,000 per patient).[19] Across all development phases, the increase was 70 percent. The report notes that finding a sufficient number of general clinical sites is a challenge, but that "the biggest driver behind higher vendor costs and site recruitment issues is an increasingly intense competition for top-performing investigator sites."

One source of cost in any trial is the number of data elements that are collected. Another approach to reducing trial costs involves "large, simple trials."[20] Such trials have the potential to reduce costs by simplifying eligibility criteria and reducing the number of outcomes tracked. No statutory or regulatory barrier precludes adoption of such trial designs. Rather, a participant in an IOM workshop described the barrier as risk aversion, with researchers preferring to collect 100 unnecessary variables than to miss one important one.[20]

Registries

One successful large simple trial randomized patients through use of an existing cardiovascular disease registry in Sweden. Registries are large databases that collect information on groups of patients treated for a particular medical condition. The TASTE trial enrolled more than 7,000 patients, and—in unprecedented fashion—allowed investigators to keep track of every patient throughout the course of the research at a total cost of $50 per patient, or only $300,000 for the entire trial.[21] Conducting a traditional study of this size in the United States would cost hundreds of millions of dollars, if not more.

Registries have been used to a limited extent in the United States to expedite patient access to new products. Notably, the FDA has approved an expanded indication for an innovative heart valve based on data from an existing registry, in lieu of a randomized clinical trial. Pew, together with the Blue Cross Blue Shield Association and the Medical Device Epidemiology Network, convened experts from the medical device industry, the registry community and government to consider how to achieve the full potential of registries in a financially sustainable way.[22]

Several barriers exist to fully achieving the promise of registries. Despite the dramatic uptake of electronic health information sources, these systems cannot easily transmit data among one another. This lack of interoperability, for example, hinders the ability of registries to extract clinical and outcomes data from EHRs. Instead, registries must develop the ability to extract information from the EHR systems at each facility, or require manual entry from providers. Additionally, many registries have sought clarity on when their studies are considered research, rather than quality improvement efforts. This confusion has slowed their use by hospitals and their ability to make a meaningful contribution.

Post-market data and expedited device approval

Better post-market data—from registries and other sources—would facilitate more effective FDA regulation across the total product life cycle. For example, FDA has proposed an expedited access premarket approval policy for devices that fill serious, unmet medical needs. Under this program, FDA would implement a total-product-life-cycle approach to regulation by accepting more uncertainty on some of the effects of new products and require the answers to those questions from post-market studies. As a result, FDA could accept smaller trials and the use of surrogate endpoints or short follow-up on patients in the premarket setting, with additional data collected after approval. This approach—so long as it remains tailored to only those devices that will significantly improve the options available for patients with serious conditions—can help reduce the time to market of new products without sacrificing the data collected on the products.

"Real world" and post-market data

As FDA continues to implement a total-product-life-cycle approach to regulation, better post-market controls and data can provide assurances that any problems not detected by clinical trials

are promptly identified after approval. The FDA may be reluctant to approve products more quickly if the agency is not confident that safety problems will be detected in the post-market setting. At present, the ability to assess product performance based on claims, electronic health record and registry data is extremely limited (see, for example, Madigan *et al.*'s description of varying results depending on the choice of database).[23]

As previously stated, developing the infrastructure to more efficiently collect and evaluate such information could substantially reduce the long-term cost of acquiring clinical data. It may also allow for evaluation of products across a wider range of conditions and patient populations. However, it is important to note that building this capacity will require investment in both infrastructure and methods development.

Along with the use of registries to gather this information, systems such as the FDA's post-market surveillance Sentinel Initiative can provide better longitudinal data on product performance. Sentinel, a distributed database that includes data from 178 million individuals, illustrates the potential of real world evidence, but also its challenges.[24] The FDA already uses Sentinel to evaluate drug safety, and Congress instructed the agency to expand this initiative to devices. However, the Sentinel program relies primarily on claims data, which lack information on the specific device used in care. If integrated into claims, the new unique device identifier (UDI) system can provide that specificity by clearly indicating the manufacturer and model of the device used. The Centers for Medicare & Medicaid Services must issue regulations to update the claims form to include this information so that FDA can utilize Sentinel—in accordance with the congressional directive—to evaluate device safety.

In addition, a report released last month from a multi-stakeholder group of medical device safety experts recommended several reforms and investments to support more robust data on the performance of new technologies after approval. For example, the National Medical Device Post-market Surveillance System Planning Board endorsed the inclusion of documenting UDI in claims to develop better data on the long-term performance of medical devices. In addition, the Planning Board recommended the development of a public-private partnership to advance, oversee and coordinate efforts to evaluate the quality of marketed devices. Congress should evaluate the Planning Board proposal and encourage all stakeholders--including FDA, CMS, manufacturers, clinicians and health plans--to develop a more robust post-market surveillance infrastructure.

Systemic FDA challenges

FDA's most important resource is its staff, including physicians, statisticians, scientists and biomedical engineers that review medical product applications, data from clinical trials and post-market information.

A 2012 Pew-funded report from the Partnership for Public Service (PPS) found several challenges to FDA's hiring, recruitment and retention of these scientific and medical experts. PPS recommended that FDA develop targeted recruitment programs to fill its talent pipeline, invest in career training and leadership development programs, and implement strategies to reduce attrition rates.[25]

Perhaps the most commonly cited measure of FDA performance is drug approval time. Recent studies have demonstrated that FDA approves drugs more quickly than regulators in Europe and Canada.[8,26] Moreover, median time to approval today is substantially lower than prior to the implementation of PDUFA goals.[27] Over recent decades, the overall success rate for New Drug Applications (NDAs) has been relatively consistent (averaging 79% from 1993-2012), but the share of drugs approved at the first action date has increased markedly (45% over 20 years, but 77% in 2011-12).[28] To a large extent that is a function of the quality of the applications.[29] FDA has some capacity to influence submission quality through its communication with industry, either during individual meetings or through guidance documents. According to a recent PwC survey of industry executives, 78% responded that FDA has improved the quality and frequency of its communications with industry over the last two years, and 76% responded that the agency provided "actionable feedback."[30]

Successive FDA user-fee agreements have provided the agency with resources to facilitate the evaluation of medical products and have established new FDA performance metrics and formal mechanisms for interaction between the FDA and sponsors. Nevertheless, a frequently cited barrier to medical product development is an absence of predictability in the FDA's regulatory review processes.[31-34] As part of negotiations to reauthorize the prescription drug and medical device user fees through the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), both industries highlighted improving regulatory predictability as a major goal and, in the case of devices, a "paramount" concern.[35,36]

Regulatory predictability may be defined as agency decisions that are not arbitrary, arrived at through transparent procedures, consistently enforced, and free of bias.[37] However, discussions about regulatory predictability frequently lack specificity. Efforts to assess or improve predictability may be confounded by the complex scientific and regulatory environment in which drug and device regulation occurs. Moreover, this environment is not static; no two products are exactly alike, and the understanding of disease changes and improves over time, as does the science of evaluating product performance. And science itself is unpredictable: the act of evaluating a product may generate information that raises further questions or undermines confidence in the outcome of a study, thus requiring further investigation. Fundamentally, regulatory decisions involve value judgments about the acceptable level of uncertainty in the data used to assess both safety and efficacy.

An upcoming Pew report summarizes the results of an industry survey and expert conference with industry and FDA leaders on predictability. The survey showed concern about FDA processes and timing, but found that a large majority agrees with FDA's ultimate decisions – saying the FDA makes the appropriate decision on new medical products "most or all of the time." In addition, about 62 percent of the respondents said FDA's data requirements are necessary in "all or more cases," with only two percent saying the requirements were necessary in "very few cases."

When probed further, most respondents to the survey as well as workshop participants expressed concerns regarding the agency's predictability. Thirty-eight percent of industry respondents said, based on their personal experiences, that the FDA's regulatory review process is "completely or fairly" predictable (higher among biotechnology and pharmaceutical professionals and lower among medical device professionals). The discrepancy among drug versus device executives was a consistent pattern, perhaps attributable to the greater diversity of medical devices products and companies and the breadth of approaches to testing their safety and efficacy, as well as staffing issues within CDRH, which the division acknowledged.

Overall, 68 percent of respondents said that such unpredictability discouraged the development of new products. A third (36 percent) said the agency strikes the right balance between speed and safety. Industry professionals were divided on the degree to which they believed the system needs to be fixed. Nearly half (49 percent) believe the agency's product review systems need a "complete or major overhaul." The same number said the systems worked "fine as-is" or needed only "minor modifications."

It is important to recognize that regulatory predictability is a broad and subjective term used to describe a variety of issues. Therefore, attempts to solve "regulatory predictability" are less likely to succeed because the problem itself is not defined precisely enough. Rather than relying on this broad diagnosis, stakeholders would be better served to articulate issues regarding, for example, communications, staff experience, or data accessibility.

To aid in that process, we briefly characterize several of these commonly cited facets of unpredictability and potential solutions to address them. These proposals reflect ideas raised by sponsors, FDA officials, analysts, researchers, and other stakeholders during the course of our research:

- Establishing clear data requirements;
- Inconsistency among FDA reviewers and review divisions;
- Issues related to the publication of guidances;
- Data integration and accessibility; and
- Sponsor inexperience with regulatory review.

Sponsors sometimes assert that there is often a lack of clarity or explicit rationale regarding the type and quantity of additional safety and efficacy data that FDA staff requests. Specifically, several sponsors asserted that such requests are manifestations of an inherent and unwarranted "risk-aversion" on the part of FDA staff. Sponsors assert that some officials lack an understanding about how much risk the agency is willing to tolerate. As they submit documents to the agency, FDA staff will request additional information to address possible concerns with a product or learn more about how a drug will affect patients. Sponsors contend that many of these data requests would negligibly affect FDA's decisions but are burdensome and expensive. Similarly, they assert that some data requests are too academic and not germane to the safety and efficacy of a product.

Current and former FDA officials we spoke with contend that the FDA must maintain some measure of flexibility when evaluating sponsors' applications. Over the course of a product's lifecycle new information may become available – from the scientific literature, from its regulatory counterparts in other jurisdictions, among other places – that compels the FDA to look at a sponsor's application in a new light. Moreover, in the course of reviewing applications from other sponsors on a similar product, and through post-marketing surveillance monitoring, FDA reviewers identify potential safety and efficacy issues with a product class and uses that information to make additional data requests of sponsors. Because specific reference to other sponsor's applications is prohibited by commercial confidentiality laws, FDA staff cannot always be specific about the reasons underlying a particular data request, leading to sponsor perceptions of FDA capriciousness or arbitrariness.

To achieve greater predictability, our conference found substantial support for the suggestion that the FDA should release all documents—such as Complete Response Letters—that provide information on why the agency requested additional information or declined to approve a product. (Complete Response letters are effectively the FDA's communication to a sponsor of why a product is not approved; currently the FDA does not release these letters publicly.) That information will help all companies understand the data sought for certain diseases and about classes of medical products.

Most respondents (78 percent) suggested that investing in human resources, such as training staff, would be a "fairly" or "very" effective strategy for improving FDA's review process, making this the most popular proposal offered in the survey.

The FDA's centers for drugs and devices both have established a number of programs and pathways that facilitate earlier and more frequent interactions between sponsors and agency staff. When meeting with the FDA about adaptive trial designs or other issues that are not typical for a standard drug application, sponsors should request the attendance and input of senior FDA

leadership. Such input could provide needed reassurance to reviewers and assuage their concerns with a product review.

Inexperience submitting products for FDA review leads to sponsors maintaining inaccurate expectations about data requirements and agency processes, ultimately resulting in perceptions of unpredictability when those expectations are not met. Small companies are especially susceptible to this problem. A study by Booz Allen Hamilton found that large companies obtain approval on their original submission 58 percent of the time, whereas that is true for only 41 percent of small company submissions.[29] More recently, a PriceWaterhouseCoopers survey found that large companies were more likely to avail themselves of interactions with the FDA; smaller companies were more likely to rely on guidance.[30]

Sponsors that have not previously submitted products to the FDA for review may lack an accurate understanding of the data requirements and agency processes. Moreover, many small companies fail to hire experienced consultants and regulatory experts to assist with product submissions. Without this help, companies may submit inadequate or noncompliant submissions to the FDA.

Other measures provide insights on additional aspects of agency operations, such as presentations to societies, consortia, industry and government organizations (around 100 per month for the center for drugs).[38] Of particular interest may be issuance of FDA guidance documents, which serve to communicate the agency's current thinking on specific topics. The center for drugs, for example, issued 51 draft guidances in 2014, but only 13 final guidances.[39] Earlier years follow a similar pattern. The reasons for this discrepancy are unclear. It may be that the agency seeks a wide range of input during development of a draft guidance, which then serves as an effective tool for communicating with stakeholders. Alternatively, it may be that the process for administrative clearance deters the agency from finalizing guidances. Congress could evaluate the balance between finalizing guidances and the potential opportunity cost of fewer new draft guidances on other topics, and potentially identify administrative simplifications that would facilitate finalization. A similar investigation of the time required to develop and finalize a formal FDA rule (often several years) might lead to solutions that would support greater overall efficiency.

Regulatory science and public private partnerships

FDA has focused on the need for better tools to inform its decision making at least since the Critical Path report in 2004, and more recently through its Regulatory Science strategic plan and associated initiatives.[40] The regulatory science rubric is used by the agency and stakeholders to refer both to the development of tools and approaches for use by sponsors and to the development of approaches the agency may use in decision making.

Pew's predictability survey found strong support for investment in regulatory science as a "very or fairly effective" means to improve the review process.

Mittleman *et al.*[41] provide an excellent overview of the opportunities for precompetitive consortia, noting both their potential and the need for more investment. They find that these organizations succeed by bringing together industry, academics, government and mission-driven non-profits to deliver on separate and shared interests. However, these organizations require time and resources to produce results. For example, the Biomarkers Consortium took nearly two years of negotiations to bridge the divergent standards and practices, including IP considerations, of various stakeholders. That organization has now initiated 15 projects, with its first completed in 2009. In contrast with the $2.7 billion European investment in the Innovative Medicines Initiative, US support of the various consortia has been limited.

While universities and government are not configured to develop medicines, public-private partnerships have the potential to spur innovation. For example, Pew's focus on antibiotic development has shown that there are key scientific questions that could underpin a resurgence in antibiotic discovery, but are currently the province of neither industry nor academia. One barrier to progress, or at least to efficient progress, is that academic scientists may not have complete information about what avenues have been pursued by other researchers, particularly those in industry. Even where needs are clear, there are limits to the ability of current research funding mechanisms to encourage progress on the most fundamental questions.

Pew has convened experts to identify barriers to scientific breakthroughs in antibiotic drug discovery and develop a roadmap for addressing them. That process is ongoing, but initial discussions have identified factors such as inter-disciplinary expertise, co-location, common mission/goals, and sustained funding efforts as crucial for making headway. These are features that may be difficult to capture with traditional "bottom-up" funding mechanisms.

Conclusion

The medical products ecosystem continues to produce innovative products that, in aggregate, benefit Americans and improve health. Products with the greatest potential to address unmet medical needs enjoy a variety of advantages that speed development and review. The FDA, lawmakers, industry, clinicians, patients, venture capitalists, and other interested stakeholders share complementary goals: ensuring that patients have access to safe and effective novel medical products and enabling U.S. companies to stay competitive.

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