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BEFORE THE SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES
LEGISLATIVE HEARING ON DISCUSSION DRAFTS CONCERNING
PRESCRIPTION DRUG USER FEE ACT REAUTHORIZATION,
MEDICAL DEVICE USER FEE AND MODERNIZATION ACT
REAUTHORIZATION, DRUG SAFETY, AND CERTAIN PEDIATRIC
PHARMACEUTICAL AND DEVICE LEGISLATION

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A. Introduction

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify today on the discussion drafts intended to reauthorize the Prescription Drug User Fee Act (PDUFA), further ensure the safety of the nation's drug supply, and reauthorize important provisions facilitating pediatric research, i.e., the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

My name is Caroline Loew, Ph.D., and I am Senior Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, also known as PhRMA. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Our member companies invested more than \$43 billion last year in discovering and developing new medicines for American patients. It is thus no overstatement to say that PhRMA companies are leading the way in the search for cures.

PhRMA and its member companies consider reauthorization of PDUFA, drug safety, and reauthorization of BPCA and PREA to be top priorities. PhRMA appreciates the opportunity to provide our views to this Subcommittee on these critical issues.

B. Reauthorization of PDUFA

Reauthorization of PDUFA is one of the more important legislative issues facing Congress this year. Since its enactment in 1992, PDUFA has brought about tangible benefits to patients, the FDA, and the pharmaceutical industry. FDA's appropriated resources have been augmented by industry user fees, providing the Agency with

sufficient resources to conduct reviews of new pharmaceuticals in a thorough and timely manner assuring widespread patient access.

Since its original passage in 1992, PDUFA has been a crucial program not only for FDA and the pharmaceutical industry, but also – and most importantly – for patients. By leveraging industry user fees, FDA has been able to review and act on new drug applications (NDA) and Biologic License Application (BLAs) in a timely manner. Life-saving medications are routinely available to patients within six months of submission of the NDA, an important public health achievement. Widespread access to new cancer and HIV medicines has markedly improved the outlooks for patients suffering from these diseases.

Throughout the PDUFA programs of the past 15 years, the exacting standards by which FDA evaluates NDAs and BLAs have not been altered. What has been altered is the level of resources available for FDA to perform its critical function of reviewing safety and effectiveness of potentially life-saving medications. Funds go to FDA's general drug and biologic budget and simply are used to hire additional staff to allow FDA to perform its critical drug review functions while maintaining the same exacting standards for safety and efficacy (demonstrated by the fact that the drug withdrawal rate pre- and post-PDUFA has remained constant at just over 3%).

The FDA's PDUFA-IV proposal is no exception to this approach, and contains important new provisions and resources to:

- enhance and modernize the FDA drug safety program,
- add a new user fee program to give FDA additional resources to review and provide advisory opinions on direct to consumer television advertisements,

- improve drug development, and
- provide more stable financing for the program.

Although the industry-funded part of the drug review process will increase during the PDUFA-IV years, patients will be well served by a more predictable drug review process and assurance that the robust drug safety office within the Agency will be enhanced and modernized.

The substantial new funding provided to enhance and modernize the FDA drug safety system – nearly \$150 million dollars over the next five years – will continue to assure that FDA’s pre- and post-market safety assessment system is the world’s best. These funds substantially address the relevant recommendations on FDA resources and the science of safety that the Institute of Medicine (IOM) issued last fall in their report on the US drug safety system.

These additional resources will be used to reduce FDA’s reliance on the spontaneous reporting of adverse events and increase use of modernized techniques and resources, such as epidemiology studies and large medical databases, to identify risks more quickly and accurately. FDA needs to be able to use new IT systems, access to electronic health records, new algorithms for detecting drug safety signals, as well as new approaches to validating drug safety signals. Funding is provided in the PDUFA-IV proposal to move towards this future.

The PDUFA-IV proposal also includes a new user fee for direct-to-consumer (“DTC”) television advertisements. This will allow FDA to hire 27 additional employees to review drug advertisements *prior* to public dissemination, helping to ensure that benefits and risks are clearly and accurately communicated. It also will create strong

incentives for companies to submit television advertisements to FDA before airing them, thereby directly supporting full implementation of the PhRMA *Guiding Principles on Direct-to-Consumer Advertising About Prescription Medicines* (“*Guiding Principles*”), which have been extremely effective over the past year and a half at improving the level of DTC communications.

This PDUFA proposal also continues forward with suggested improvements to the drug review process. FDA will implement the good review management principles that were formulated during PDUFA-III. FDA will communicate to sponsors a timeline for discussing labeling and post-market commitments in advance of the action date. This will improve the predictability of the drug review process and lead to more meaningful post-market studies that are appropriate for the new drug.

Funding is allocated for the purpose of increasing the efficiency and accuracy of drug development. This will permit FDA staff to be directly involved in external activities such as partnerships and consortia that are generating data and information that will create new paradigms for drug development. In return, FDA commits to developing draft guidance in areas related to safety assessment, clinical trial design, and the use of biomarkers. In addition, FDA will participate in workshops and other public meetings to explore new approaches to a structured model for benefit/risk assessment. The results of these interactions will be used to assess whether pilot(s) of such new approaches can be conducted during PDUFA-IV. Collectively, this will lead to new paradigms leading to more efficient and accurate drug development resulting in earlier patient access of important therapies.

C. Drug Safety

When considering potential drug safety legislation, PhRMA believes that Congress should keep in mind the following principles:

- The current drug safety system is robust and effective but could be made even better with additional resources and better use of modern scientific techniques and resources for identifying and assessing risks.
- Assessment of safety concerns must always be undertaken with full knowledge of the benefits (efficacy) of a drug. Drug safety is a balance between benefit and risk. This is critical as any assessment that focuses solely on risk will lead to decisions that will have an adverse impact on the public health and patients.
- Drug safety is an ongoing process that begins long before a medicine enters the marketplace and continues long after it has been made available to patients. Drug safety does not stop at approval.
- Any drug safety reforms should strengthen FDA's oversight capabilities without impeding innovation or interfering with patient access to needed medications. This is particularly important for patients with serious or life-threatening diseases and patients living in rural areas.

1. The Current Drug Safety System Is Robust

Despite recent concerns expressed about FDA's ability to ensure drug safety, it is important to recognize that FDA's current drug safety system is robust and effective. From the approval process through post-market surveillance, the system is working well. This is reflected in the fact that over the last 20 years, about 97 percent of prescription

medicines approved for patient use in the U.S. have safely remained on the market, while only about 3 percent of medicines have been withdrawn for safety reasons.

Before a drug is ever allowed on the market, it must undergo a rigorous pre-market testing and approval process that often spans between 10 to 15 years. Drug safety testing starts early in the development process through a series of laboratory tests, animal tests, and then with very small numbers of volunteer patients, and continues through large scale Phase 3 clinical trials involving on average several thousand patients. Because the science is constantly evolving, pre-approval safety testing is much more rigorous today than it was even ten or fifteen years ago. Companies now routinely test for safety issues that once were poorly understood, could not be predicted well, and for which there were no accurate tests. For instance, today a company will often assess whether a drug causes QTc interval prolongation, a rare but serious side effect which could cause heart arrhythmia, and similarly will often assess the liver toxicity of a drug, which is again a rare but serious side effect associated with some drugs. As a result, we typically know far more about the safety profile of a drug that is approved under today's standards and science than ever before.

The FDA's post-market surveillance system also is robust and constantly improving. Once a drug is approved, safety is monitored continuously as long as it is on the market through a collaborative process involving FDA, pharmaceutical companies, healthcare providers and patients. Physicians, nurses, and other healthcare providers are on the front-line of drug safety; they are often the first to learn of a potential problem with a medicine and are encouraged to report issues or concerns promptly to the FDA or the company concerned. Companies likewise play a critical role in assessing new and

emerging risks with marketed medications, with dedicated teams of experienced physicians and scientists whose job is to collect and analyze safety data on a daily basis, and to immediately report any potential problems to government authorities.

2. **PhRMA Supports the Safety Improvements In PDUFA and Carefully Targeted Revisions to FDA's Authority**

Although the current drug safety system is robust, even a good system can be made better. PhRMA believes that FDA's drug safety system could be significantly improved with additional resources and a more modernized approach. FDA's most urgent need is not additional authority; rather, FDA needs additional resources devoted to drug safety activities and an approach that takes full advantage of the latest scientific tools and resources.

The FDA's proposal to reauthorize PDUFA, as discussed above, includes significant new funds for FDA to enhance and modernize the drug safety system. The PDUFA-IV proposal provides approximately \$150 million over five years to allow FDA to (1) hire 82 additional staff for drug safety activities, including experts in epidemiology; (2) increase use of modernized techniques, such as epidemiology studies and large medical databases, which contain a wealth of drug safety information; and (3) reduce FDA's reliance on spontaneous adverse event reports. The PDUFA-IV proposal also removes the three-year time limitation so that FDA can use funds from the user fee program to address safety issues whenever they emerge.

PhRMA believes that the robust drug safety provisions in the PDUFA-IV proposal address FDA's drug safety needs. These new provisions, along with FDA's own internal reforms, should be allowed to work to enhance and modernize the drug safety system. We are concerned that adding significant new authorities and a markedly

different review paradigm, such as the Risk Evaluation and Mitigation Strategy (REMS) proposed in the discussion draft, may actually be counter-productive. The REMS process creates a complicated and bureaucratic safety oversight system that may not be workable in practice. These additional processes may end up impairing drug safety oversight by miring FDA safety officers in unproductive bureaucratic exercises rather than meaningful safety surveillance activities. They also will add significant costs to the drug development process, thereby impairing innovation and impeding access to life-saving medications. This is particularly the case as the REMS process envisioned in the House discussion draft will be applied to all drugs, rather than targeted at those showing safety signals that warrant more rigorous post-market safety monitoring. At the very least, targeting use of the REMS, and hence limited FDA resources, on higher risk products would be a more appropriate approach.

If Congress believes that the drug safety enhancements in the PDUFA-IV proposal are not sufficient and that FDA needs additional authorities, this should be accomplished through carefully targeted revisions to the Federal Food, Drug, and Cosmetic Act (“FFDCA” or “the Act”). While PhRMA believes that FDA’s existing authorities are sufficient to ensure compliance with all applicable regulatory requirements, PhRMA nevertheless would support targeted revisions to the Act to clarify FDA’s authority provided such revisions do not impede innovation or interfere with patient access to needed medications. Significantly, the targeted revisions discussed below can be accomplished *without* creating an entirely new bureaucratic maze. In particular, PhRMA would support the following revisions:

Clinical Trial Registries and Databases. PhRMA and its member companies are committed to the transparency of clinical trial information. Consequently, PhRMA supports a federal requirement that companies post information about ongoing clinical trials to a registry to assist patients who might want to participate in a trial. The registry, however, should be limited to hypothesis-testing trials and should not require the public dissemination of confidential commercial information.

In addition, PhRMA supports a federal requirement that companies post the results of completed studies to a national clinical trial results database. Like the registry, the results database should be limited to hypothesis-testing trials, which provide meaningful information that could be used to guide prescribing decisions. Moreover, the database should be limited to information about drug products that have been approved for at least one use, since physicians cannot prescribe drugs that have never been approved and are not on the market.

Postmarket Study Authority. PhRMA supports granting FDA explicit statutory authority to require a post-marketing study if, on the basis of new scientific information obtained after a drug is approved, FDA determines that (a) the drug may be associated with a significant new risk not listed on the current approved labeling; (b) a post-marketing study is necessary to assess the significant new risk; and (c) the information expected to be obtained from the post-marketing study would make a material contribution to the approved labeling for the drug. Moreover, the new authority should be limited to significant new risks associated with an approved use of the drug. Although physicians should remain free to prescribe a drug any way they deem appropriate as a legitimate exercise of the practice of medicine, companies should not be required to

conduct research on a use they have not and do not intend to market. Finally, post-marketing studies can be extremely burdensome for sponsors and, in many cases, may be unnecessary to mitigate risks posed by a drug. Sponsors should have the option to take other equally effective but less burdensome actions (e.g., label change) before being ordered to conduct a post-marketing study.

Labeling Authority. PhRMA supports proposals that give FDA greater authority to require a labeling change when warranted. PhRMA also supports the creation of an accelerated dispute resolution process for label changes that maintains the ability of the sponsor and FDA to engage in a meaningful scientific dialogue but also places time limitations on such dialogue to ensure that new safety information is included on the approved labeling in a timely manner. Finally, PhRMA supports the requirement that FDA review and approve all safety labeling changes prior to implementation within 30 days of submission. This will ensure that the FDA-approved labeling remains the primary source of information about a drug product and that safety labeling changes not subject to the dispute resolution process are implemented in a timely fashion.

Distribution and Use Restrictions. PhRMA supports clarifying FDA's authority to approve drug products subject to certain distribution or use restrictions. However, because distribution and use restrictions create significant limitations on patient access to needed medications, they should be imposed only in exceptional circumstances. PhRMA is concerned that providing FDA explicit statutory authority to impose distribution and use restrictions could lead to the routine use of very onerous restrictions that should be reserved for exceptional circumstances. This not only would interfere with the legitimate practice of medicine but also could unnecessarily limit drug availability, particularly in

rural areas, to the detriment of patients. Consequently, any such authority should be limited so that it can be used only when absolutely necessary to ensure safe use of the product. Finally, distribution and use restrictions applicable to an innovative drug should likewise apply equally to any generic copy of the drug.

3. **Specific Concerns with Discussion Drafts**

PhRMA wants to work with FDA and all stakeholders to improve the already robust drug safety system in a meaningful way that preserves innovation and patient access. While we believe there are flaws with the REMS proposal in the current discussion draft and would prefer an approach that relies upon more targeted revisions (as discussed above), we are providing the following comments under the assumption that there is a continuing commitment to the REMS structure. These comments are provided in an effort to help ensure the proposed legislation accomplishes its goal of enhancing the drug safety system without impairing innovation or patient access to life-saving medications.

Preemption. The REMS and other discussion drafts contain an express anti-preemption provision stating that nothing in the Act “may be construed as having any legal effect on any cause of action for damages under the law of any State (including statutes, regulations, and common law).”

This anti-preemption provision would undermine the REMS bill’s purpose of reinforcing the FDA’s control over drug warnings because it would enable each state to require warnings (or punish manufacturers for not adopting warnings) that the FDA *specifically rejected* after determining that they have no basis in science. FDA’s role under the REMS process is to ensure that labeling is scientifically appropriate and

justified, and accurately and succinctly communicates all relevant safety information in a manner that neither understates nor overstates the risks for a particular product. While understatement of a risk can hurt patient safety, overstatement of a risk can deter otherwise beneficial and appropriate use of a medicine by patients who would clearly benefit. The anti-preemption provision would undermine FDA's primacy in determining the proper complex balance to strike by permitting state judges and juries – in each of the 50 states – to require (and punish companies for not providing) warnings that FDA has determined through the comprehensive REMS process are unsubstantiated or scientifically unjustified. The result would be conflicting warning requirements that would confuse the public, force manufacturers to choose between violating federal or state law, and frustrate the REMS bill's primary purpose of strengthening the FDA's authority over drug labeling.

The anti-preemption provision also would frustrate the REMS bill's safety evaluation and review process. The regime encouraged by this provision would create a strong incentive for manufacturers to overload the FDA with proposed labeling changes so they can avoid liability under inconsistent state labeling requirements. Under the REMS process, FDA would have to consider each of these submissions under the aggressive timelines set forth in the REMS bill and make a determination whether to accept the proposed labeling -- even if the FDA had previously rejected the same or similar labeling as scientifically unjustified. Repeated consideration of such a flurry of submissions designed principally to avoid liability under inconsistent state standards -- not to protect public health -- would thus divert the scarce FDA resources away from the Agency's principal mission of identifying and evaluating emerging and serious safety

considerations that the Agency has not previously addressed. The Supreme Court has previously ruled that flooding the FDA with unsubstantiated submissions designed only to avoid state liability would significantly frustrate the public safety mission of the FDA. The anti-preemption provisions in the various discussion drafts thus should be removed.

Broad Scope of REMS. The proposal to require a REMS for every newly approved drug or biologic creates burdensome, bureaucratic processes for routine risk management measures, such as Dear Doctor letters and labeling changes. The proposal should be structured in accordance with the current FDA position that, for most medicines, routine risk minimization measures, such as approved professional labeling and routine adverse event monitoring and reporting, would be sufficient to achieve a favorable benefit-risk balance, and thus a specific REMS would not be required. Since these routine risk management measures already are required under the FDCA, there is no reason to require the submission of a REMS for most drug products. A REMS should be required only when the product poses a clinically important and unusual type or level of risk, and routine risk minimization measures are not sufficient to ensure the product is safe when used in accordance with its labeling.

As currently structured, if a drug sponsor wanted to issue a Dear Doctor letter, for example, it could be required to submit a full-blown REMS assessment and modification proposal to FDA. The sponsor would then have to wait for formal FDA review and the issuance of an "order" before sending its Dear Doctor letter. Clearly, this type of bureaucratic process is not necessary for routine risk minimization measures and could have the perverse effect of delaying the communication of important safety information to healthcare professionals and the public.

While the current proposal includes a provision allowing waivers of the REMS requirement, the standard is so high as to be virtually unattainable. In particular, a waiver may be granted if there is “substantial evidence that the waiver will not pose a risk” to anybody who might use the drug for its approved use. First, the standard requires the applicant to prove a negative, i.e., that the waiver “will not pose a risk.” Second, it requires “substantial evidence” to prove the negative, which has been interpreted by FDA as requiring two adequate and well-controlled clinical trials (i.e., Phase 3 trials). Clearly, this hurdle to obtain a waiver will rarely, if ever, be attained. Rather than require REMS for all products with the option of an illusory “waiver,” the REMS requirement should be structured so that it is reserved only for those products posing a clinically important and unusual type or level of risk for which routine risk minimization measures are inadequate.

Civil Money Penalties. The REMS discussion draft grants FDA sweeping new authority to impose civil monetary penalties (CMPs) for any violation of the FFDCFA. Under the proposal, a person or entity could face fines as high as 10 per cent of a product’s annual U.S. sales or \$1 million, depending on how long the product at issue has been on the market. These dollar amounts, which could reach tens or even hundreds of millions of dollars, are extraordinary. By contrast, the civil penalties in current law for drug sample diversion are \$50,000 for the first two violations in a 10-year period, escalating to \$1 million only when subsequent violations in that period, and there is no reference to annual product sales.

These extraordinary penalty levels are especially troubling given the broad and subjective nature of many of the requirements of the FFDCFA. For example, an adulteration violation can be based on failure to meet “current good manufacturing

practices,” a requirement FDA has asserted is always evolving and that is highly subjective at best. Advertising and promotional violations likewise are notoriously subjective. These extraordinary penalties will create perverse incentives regarding enforcement of the FDCA and may make it difficult or impossible for a company to defend itself with the threat of massive CMPs hanging in the background. Furthermore, the impact of such high penalties on smaller and mid-sized companies, which may have only one or two marketed products, could be significant.

Submission of Marketing Plans. The REMS discussion draft grants FDA the authority to require, as part of its review of a REMS, submission of the marketing plan for the drug under review. This unprecedented requirement is ill-defined and ill-advised. It is inappropriate for FDA to review a company’s internal competitive plans except in the most extraordinary of circumstances. The plans will not provide FDA helpful information to address the challenges of risk management, and will at best divert the agency’s attention from the scientific and data driven issues on which it should be focusing.

To the extent that a company’s internal plans have any relevance to the REMS requirements, it is only when those plans translate into the actual promotional communications a company makes in the marketplace. FDA already has sufficient tools to address this issue under current law, which requires that all advertising and promotional materials be submitted to the agency. In addition, a new proposal put forward by FDA will create a system for prior FDA review of consumer advertisements. Where those actual promotional pieces are misleading, FDA can take action under its existing enforcement authority and can otherwise consider the communication measures

of a REMS. Moreover, FDA can take enforcement action under the discussion draft if a company fails to meet the requirements of its REMS. Nothing further will be gained by creating a new mechanism for agency review of a company's internal plans.

It is inappropriate for a regulatory body to be charged with routine review of internal business planning documents. FDA has neither the experience nor the resources to review internal market analyses and other components of commercial planning materials on a regular basis. Moreover, by granting FDA the power to revise a REMS based on a marketing plan, the proposal essentially gives the agency the power to review *and approve* these internal company documents. Absent extraordinary and highly compelling reasons, neither FDA nor any other agency should be charged with the extreme measure of overseeing the internal affairs of the private entities it regulates.

Post-Approval Study Authority. The discussion draft gives FDA broad authority to request post-market studies (e.g., observational studies) and post-market clinical trials, both before and after approval. The standard for requiring studies or trials is extremely low and could result in mandatory post-marketing commitments for virtually all drugs, studies which in many cases would likely be unnecessary and a diversion of both FDA and company resources from other more important activities. Under the bill, studies could be required if adverse event reporting is not sufficient to assess a signal of a serious risk or identify unexpected serious risks in unstudied populations (e.g., children, elderly). This standard gives FDA virtually unlimited discretion to order studies because the requirement can be triggered by a single serious adverse event – *or even by no adverse event at all*. For example, FDA could order a sponsor to conduct multiple studies

searching for evidence of a serious adverse event that had never been observed in any population, i.e., an “unexpected” serious risk.

PhRMA believes that studies should be required only when scientifically and medically justified, not based upon administrative whim or the desire to go on adverse event “fishing expeditions.” Requiring unnecessary studies will harm innovative research and development activities while generating little useful information for prescribers and patients. The standard should be revised to permit FDA to require a post-approval study only when new scientific information suggests that the drug may pose a significant new risk not adequately reflected on the approved labeling and the information derived from the study is expected to yield meaningful information for patients and prescribers.

In addition, the draft should provide explicit exemptions from the REMS sanctions provisions when studies cannot be completed due to circumstances beyond the sponsor’s control. Post-market studies may be impossible to complete for a variety of reasons that have nothing to do with the sponsor’s good-faith efforts. For example, a sponsor may experience unforeseen enrollment difficulties due to subsequent approval of a competing product, or the study may no longer be needed because of advancing science. Sponsors should not be subject to sanctions under these circumstances.

Advertising Restrictions. The bill provides FDA with sweeping new authority to limit advertising for prescription drugs in ways that will interfere with the free flow of truthful and accurate information about prescription drugs in violation of the First Amendment. FDA acknowledges that DTC advertising can benefit the public health by “informing patients about the availability of new treatment options and encouraging

patients to see a physician about an illness for the first time.” 72 Fed. Reg. 1752 (Jan. 16, 2007). DTC advertising also encourages dialogue between physicians and patients and promotes improved compliance with physician-prescribed treatments. The restrictions that could be imposed under the bill have the potential to harm the public health by reducing or eliminating these public health benefits, particularly with respect to new treatments for patients looking for better options.

Moreover, the standards for imposing the various advertising restrictions in the bill are extremely vague and set a low hurdle for FDA. For instance, a three-year moratorium can be imposed if FDA decides that it is “necessary to protect public health and safety.” Likewise, mandatory pre-clearance can be imposed if FDA decides that it is “necessary to ensure compliance with section 502(n)” regarding the disclosure of serious risks. There is no guidance as to when or why a complete ban on truthful and accurate DTC advertising would be “necessary to protect public health and safety” or when or why pre-clearance would be needed to enforce section 502(n), which already is enforceable through the Agency’s authority to punish misbranding violations. These standards amount to no standards at all and will permit FDA to impose extremely onerous advertising restrictions virtually at will.

Distribution and Use Restrictions. The bill gives FDA authority to impose distribution and use restrictions when necessary to assure safety. This provision raises several major concerns.

First, distribution and use restrictions create significant limitations on patient access to needed medications. Consequently, they should be imposed only in exceptional circumstances. PhRMA is concerned that providing FDA explicit statutory authority to

impose distribution and use restrictions could lead to the routine use of very onerous restrictions that should be reserved for exceptional circumstances. This not only would interfere with the legitimate practice of medicine but could unnecessarily limit drug availability, particularly in rural areas, to the detriment of patients. The standard for imposing distribution and use restrictions should be raised to help ensure that onerous distribution and use restrictions would be used only when absolutely necessary to ensure safe use of the product.

Second, the bill inappropriately places the responsibility for policing physicians and pharmacists on drug sponsors rather than the relevant federal and state authorities. The bill gives FDA the authority to require individual companies to monitor physicians and pharmacists and enforce compliance with distribution and use restrictions. Although companies sometimes agree to help facilitate compliance with distribution and use restrictions through, for example, education programs, the bill goes far beyond the normal scope of a company's responsibility to monitor the downstream use of its products – and far beyond most companies' capabilities to do so. The bill essentially shifts enforcement responsibilities from the appropriate federal and state authorities (e.g., FDA, Boards of Pharmacy) onto individual companies. It also forces companies to interfere with and regulate both the practice of pharmacy and the practice of medicine. These responsibilities are inappropriate and should be removed from the bill. The new “implementation” requirements not only interfere with the legitimate practice of medicine but also could create increased product liability exposure for sponsors.

“Black Triangle” Requirement. The REMS discussion draft requires, for the first two years after a new drug or indication is approved, that the labeling of that drug

and any DTC advertising include a “unique symbol indicating the newly approved status of the drug or indication.” FDA considered a similar requirement in December 2000 — a black triangle on new drugs for three years following approval — and, following a five-year public stakeholder process, abandoned the idea on the ground that the triangle would not be “universally understood, could be confusing to the prescriber (even with a concerted educational effort) and therefore may not serve its intended purposes.” 71 Fed. Reg. 3922, 3936-37 (Jan. 24, 2006).

A special symbol is unnecessary because FDA regulations already require the drug label to bear the year of initial approval in the Highlights section. 21 C.F.R. § 201.57(a)(3) and (d)(5). Moreover, the proposed special symbol likely will have no meaning and limited practical value, because it would be included in the labeling of most prescription drugs in the market. Although it must be included in labeling for only the first two years, it is likely that labeling distributed in the first two years will remain in circulation for much longer. Moreover, because the symbol must be included whenever a drug receives approval of a new indication, even drugs that have been marketed for an extended period may be required to bear the symbol. For example, under the proposal, a twenty-year-old anti-fungal medication just approved for a new dermatological condition would be required to bear the “newly-approved” symbol. This expansive and indiscriminate use will dilute the intended value of the symbol. The special symbol requirement thus should be deleted.

Clinical Trial Registry and Results Database. PhRMA generally supports increased transparency but has the following concerns with the discussion draft.

The bill requires companies to submit, in addition to a technical summary of a study, a non-technical summary in lay language that is understandable to patients. The requirement, while well-intentioned, is unworkable. Clinical trial results are complex, nuanced, scientific documents that often cannot be translated easily into lay language. This is particularly true if the results of the study are inconclusive or have statistical limitations. Companies may find it difficult or impossible to translate clinical trial results into “lay language” without losing important details or appearing to make “promotional” claims. This, in turn, could increase a sponsor’s exposure to liability for off-label promotion and false claims violations, particularly given the explicit prohibition in the bill against the submission of information that is “promotional.” Moreover, consumers already have access to a wealth of information about the proper usage of drug products, including the FDA-approved labeling, company websites, pharmacy medical information pamphlets and from healthcare professionals. Summaries of thousands of clinical trials, many of which may be inconclusive or of limited scientific value, will not add meaningful information to the resources already available. While clinical trial results should be available to patients and consumers, they should be written for a medical audience. The requirement to submit a summary in lay language should be stricken or, at the very least, limited to situations where the study is of significant medical importance.

The bill also imposes criminal penalties against database submissions that are deemed to be “promotional.” This is unworkable because neither the bill nor FDA has ever clearly defined the term “promotional.” In fact, FDA has taken the position that the dissemination of scientific studies published in peer-reviewed medical journals can be considered “promotional” if distributed by a pharmaceutical company. Clearly, if purely

scientific journal articles written by independent third parties can be considered “promotional,” consumer-friendly summaries written by pharmaceutical companies will be subject to significantly heightened risks. Without clear standards defining the term “promotional,” companies will face unacceptable risks under the discussion draft simply trying to comply with the posting requirements. Thus, all references to the term “promotional” should be stricken from the bill. At a minimum, companies should not face criminal penalties for submitting “promotional” summaries, particularly lay summaries, unless and until FDA issues clear guidance defining the line between unlawful promotion and non-promotional scientific exchange.

Finally, the discussion draft requires disclosure of irrelevant information about drugs that are never approved or marketed for any use. The purpose of a clinical trial results database should be to provide useful clinical trial information to physicians to better inform their prescribing decisions. If a drug is never approved or marketed, it cannot be prescribed. The results database thus should be limited to information about drug products that have been approved for at least one use and are available for prescribing in the U.S.

Definitions. The definitions of “serious adverse drug experience” and “unexpected serious risk” should be consistent with the definitions of those and similar terms in FDA’s regulations at 21 C.F.R. §314.80. As currently drafted, there are significant differences, which will cause unnecessary confusion and could force FDA to revise its regulations. Unless there is a compelling reason for creating differences between the statutory and regulatory language, which is not evident, the statutory definitions should reference FDA’s current regulations or reproduce them verbatim.

REMS Decision-Maker. The dispute resolution process does not specify who within FDA must make a final decision nor does it distinguish between different types of disputes. We believe that for significant requirements, such as whether to order a large, complex and lengthy clinical trial, whether to impose burdensome distribution restrictions, or whether to impose restrictive labeling requirements, the final decision should be made at a high level within FDA. These types of requirements not only burden the specific company involved but, more importantly, can have a significant impact on the public health, the availability of drug products and the practice of medicine. Thus, disputes about post-market studies, distribution restrictions and labeling changes should be ultimately resolved at a level no lower than the Director of the Center for Drug Evaluation and Research (CDER) or the Director of the Center for Biologics Evaluation and Research (CBER).

Labeling Changes. The bill exempts labeling changes that could be made with a “changes being effected” (“CBE”) supplement from the assessment requirement of the REMS provisions. While likely not intended, the effect of this provision could be to exempt all safety labeling changes from the REMS provisions, since virtually any safety labeling revision can be made with a CBE supplement. We suggest striking this exemption.

D. Critical Path – The Reagan-Udall Institute

The FDA’s Critical Path initiative has set forward to improve the efficiency and accuracy of the drug development process through, among other things, the development and validation of new tools and technologies. These objectives, and FDA’s approach to achieving them, are something that PhRMA strongly supports. We further support the

funds for this program included in FDA's proposal to reauthorize PDUFA. This funding will permit FDA staff to be directly involved in external activities such as partnerships and consortia that are generating data and information that will create new paradigms for drug development. In return, FDA commits to developing draft guidance in areas related to safety assessment, clinical trial design, and the use of biomarkers. In addition, FDA will participate in workshops and other public meetings to explore new approaches to a structured model for benefit/risk assessment. The results of these interactions will be used to assess whether pilot(s) of such new approaches can be conducted during PDUFA-IV. Collectively, this will lead to new paradigms leading to more efficient and accurate drug development resulting in earlier patient access of important therapies.

The draft legislation proposing the establishment of the Reagan-Udall Institute will build on this foundational funding, and provide FDA a venue to conduct research in many important areas needed to improve the efficiency and accuracy of the drug development process. As such, PhRMA supports the proposal to establish this institute.

E. Pediatric Study Programs

1. History of Pediatric Exclusivity Program

Historically in the U.S., significant disincentives existed to conduct clinical trials for pediatric use (generally speaking, under the age of 16) of a medicine developed primarily for adult use. Among other factors, exposure to product liability and medical malpractice were prominent disincentives. Prior to enactment of the pediatric exclusivity provisions in the Food and Drug Administration Modernization Act of 1997 (FDAMA), there were concerns that many FDA-approved drugs had not yet been clinically tested in

children. For example, about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information.¹

Congress responded to the need for more pediatric specific information by providing incentives to encourage manufacturers to conduct pediatric studies of medicines with potential uses as medicines for children. FDAMA included a provision that granted pharmaceutical firms an additional six-month period of exclusivity, known as pediatric exclusivity, upon the completion of studies on the effects of a drug upon children that meet the terms of a written request from FDA. Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in the Best Pharmaceuticals for Children Act (BPCA) in 2002. The BPCA sunsets on October 1, 2007, unless reauthorized.

In addition to the BPCA, the Pediatric Research Equity Act (PREA) gives FDA the authority to require studies of drugs for the approved indication only, i.e., when the use being studied in children is the same as the approved adult indication. PREA gave FDA the authority to require manufacturers to conduct pediatric testing for certain new drugs and biologics and produce formulations appropriate for children, e.g., liquids or chewable form tablets. PREA applies to products that are already on the market only if FDA determines that the absence of pediatric labeling could pose significant risks and after it exhausts the possibility of funding the pediatric studies through other public and private sources. In addition, PREA also applies only if the product is likely to be used in

¹ U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

a substantial number of children or represents a meaningful benefit over medicines already on the market.

2. **Pediatric Exclusivity Program has Greatly Advanced Medical Care of Children**

The pediatric exclusivity program has been a tremendous success. According to FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative.² For example, according to the FDA, since 1997, the exclusivity incentive program has generated labeling changes for 128 products.³ A recent GAO study found that almost all of the drugs (87 percent) that had been granted pediatric exclusivity under BPCA have had important labeling changes as a result of pediatric drug studies conducted under BPCA.⁴ According to GAO, the labeling of drugs was often changed because the pediatric drug studies revealed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects.⁵ According to a February 2007 study published in the *Journal of the American Medical Association (JAMA)*, data for 59 products were submitted to the FDA between 2002-2004. Using the numbers from the labeling information for these 59 drugs, the study found that 34 percent of the time that physicians prescribed the drugs from this cohort

² “The Pediatric Exclusivity Provision, January 2001 Status Report to Congress,” FDA, 2001.

³ Statement of Rear Admiral Sandra Lynn Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, “Programs Affecting Safety and Innovation in Pediatric Therapies,” May 22, 2007.

⁴ Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act, GAO-07-557 (March 2007).

⁵ Id.

before 2002, they were making a dosing error or placing a child at risk of adverse events with limited therapeutic benefit. As the article stated, “Administration of safe drugs that work, at an appropriate dosage, is critical to public health.”⁶

Further, sponsors have submitted 504 proposed pediatric study requests to FDA, and 341 written requests have been issued by FDA to drug sponsors requesting over 703 pediatric studies.⁷ In comparison, between 1990 and 1997, only 11 products were studied in children.⁸

The public health benefits of these developments are undeniable. According to the American Academy of Pediatrics, “Pediatricians are now armed with more information about which drugs work and what doses.”⁹ Likewise, the *JAMA* study concluded, “...the greatest return of the exclusivity program is the benefits derived in obtaining new information relevant and applicable toward the care of children, and this benefit should not be compromised.”¹⁰

According to the GAO report, the most frequently studied drugs were those to treat cancer, neurological and psychiatric disorders, metabolic diseases, cardiovascular disease, and viral infections. In total, the drugs studied under BPCA are used to treat

⁶ Jennifer Li et al., “Economic Returns of Clinical Trials Performed Under the Pediatric Exclusivity Program,” *JAMA*, February 7, 2007, Vol. 297, No. 5.

⁷ Statement of Rear Admiral Sandra Lynn Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, “Programs Affecting Safety and Innovation in Pediatric Therapies,” May 22, 2007.

⁸ Jennifer Li, *op cit*.

⁹ “FDA Joins Children’s Health Groups to Mark Historic Milestone for Pediatric Drugs,” FDA Press Release, December 19, 2005.

¹⁰ Jennifer Li, *op cit*.

more than 17 broad categories of disease in children.¹¹ The range of conditions studied, the variety of drugs being studied and the nature of the scientific data all confirm that the pediatric exclusivity incentive is working and successfully meeting unmet medical needs in children.

3. Companies Continue Responding to the Incentive as Complexity and Cost of Pediatric Studies Increase

According to the Tufts Center for the Study of Drug Development (hereafter referred to as the Tufts Center), the cost, length, and complexity of pediatric studies have increased significantly since 2000. At the same time, companies have continued engaging in this important research and responding to FDA written requests at very high numbers. The GAO found that most of the on-patent drugs for which FDA requested pediatric studies under BPCA were being studied.¹² This conclusion is supported by the Tufts Center, which found an 84 percent industry response rate to FDA written requests for pediatric studies.¹³ This exceeds the 80 percent response rate expected in FDA's 2001 Status Report to Congress.

Scope, Time and Costs of Pediatric Studies Expanded Significantly in Recent Years

From 2000 to 2006, the scope of pediatric studies has expanded significantly. For example, the average number of patients per written request increased 178 percent, while the average number of studies per written request rose 60 percent.¹⁴ Additionally, the

¹¹ "Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act," GAO-07-557 (March 2007).

¹² Id.

¹³ Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

¹⁴ Id.

time required to complete pediatric studies nearly doubled between 2000 and 2006. Several factors contributed to the lengthening of study times, including increased complexity and scope of studies, as well as the availability of patients, investigators, and facilities, access to FDA staff, to name a few.¹⁵ In addition, the average cost to respond to a written request increased 8-fold from 2000 to 2006.¹⁶

Number of Efficacy and Safety Studies Grew by 60 Percent from 2000 to 2006; Most Studied New Drugs in Development and New Indications

The cumulative number of pediatric studies completed since 1998 rose from 58 at the end of 2000 to 568 at the end of 2006. Sponsors increased the proportion of efficacy and safety studies – the most expensive and time-consuming studies – from 25 percent in 2000 to 40 percent in 2006. Sponsors are continuing to break new ground – for example, 20 percent of written requests were for new drugs in development, 40 percent were for currently unapproved indications, while 40 percent were for already approved indications.¹⁷

4. The Pediatric Exclusivity Incentive Should Remain Intact

The pediatric exclusivity incentive has had a tremendous positive impact on the lives of children, but there is much more to be accomplished. For this reason, the current program – which is working well – and its basic features should not be altered. Changes in the current program could reduce the incentive to conduct pediatric studies.

Exclusivity is Not a Guarantee

¹⁵ Id.

¹⁶ Id.

¹⁷ Id.

It is important to remember that despite the incentive the pediatric exclusivity program has provided, pediatric studies are done at risk. As a preliminary matter, the FDA may determine that a company's studies do not fairly respond to the written request and therefore the company would be denied exclusivity. Further, programs may fail due to technical reasons, lack of sufficient patients, problems with study design, inadequate time to complete studies prior to loss of exclusivity, etc. Even when a company is granted exclusivity, the value of such exclusivity may be diminished (or nullified) for other reasons. Given these factors, Congress should not increase the hurdles necessary to qualify for pediatric exclusivity.

Majority of Medicines Studied by Sponsors were Not in the Top 200 Sellers; Blockbuster Drugs Receiving Pediatric Exclusivity Have Helped to Build the Necessary Infrastructure for Sustainability and Continued Growth of Pediatric Programs

Pharmaceutical companies have pursued pediatric studies for many products that are not top-selling medicines. In fact, less than half of the products that received pediatric exclusivity were in the top 200 selling drugs, according to the Tufts Center.¹⁸ Some of these include medicines for HIV/AIDS, leukemia, anti-infectives, antihistamines and anesthetic drugs. In addition, only about one-tenth of drugs awarded pediatric exclusivity were in the "blockbuster" category.¹⁹

While blockbuster drugs represent only one-tenth of the drugs awarded pediatric exclusivity, the exclusivity benefits of one blockbuster drug can support pediatric studies for other drugs and can support and expand infrastructure for pediatric drug programs.

¹⁸ U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

¹⁹ Id.

As with drug development in general, higher revenue drugs support the ability of pharmaceutical companies to invest in research for medicines with lower expected revenue. In the case of pediatrics, not only have blockbuster drugs allowed companies to invest in research for lower revenue products, they have also given companies the ability to build pediatric programs and infrastructure over the past decade. Prior to enactment of the pediatric exclusivity incentive, such infrastructure did not exist. It is important to understand that without this infrastructure, which needs to be permanent, it could impact companies' ability to conduct pediatric drug development. Unique expertise is required to develop drugs for use in children, and thanks to the pediatric incentive, companies have made significant investments in building capabilities in this area. As such, maintaining the current incentive structure will be critical to continued research in this area.

According to Dr. Floyd Sallee, M.D., Ph.D., a child psychiatrist and director of the pediatric pharmacology research unit at Cincinnati Children's Hospital Medical Center, "There was no infrastructure for the research before....Drug companies have hired pediatric experts and there is a larger network of expertise to draw from."²⁰ Dr. Sallee's comments were echoed by an industry expert, Dr. Stephen Spielberg, M.D., Ph.D., "The legislation has encouraged the development of needed infrastructure, highly specialized staffing needed to develop pediatric formulations and to perform pediatric clinical studies."²¹ Similarly, the GAO has testified that, "Experts agree that, since

²⁰ "Drug Research and Children," FDA Consumer (January – February 2003), http://www.fda.gov/fdac/features/2003/103_drugs.html

²¹ Testimony of Stephen P. Spielberg, M.D., Ph.D., before the Senate Committee on Health, Education, Labor and Pensions, Hearing on Pediatric Drug Development, May 8, 2001.

FDAMA, there also has been significant growth in the infrastructure necessary to conduct pediatric studies....The pharmaceutical industry has also increased its capacity to conduct pediatric studies since enactment of FDAMA.”²²

Revenues from top-selling products can support pediatric and adult drug research and development in other “non-blockbuster” areas. “Since research resources are allocated across drug portfolios...these medicines indeed provide the fuel to drive research and development of less remunerative compounds...”²³ Dr. Spielberg continued, “For currently marketed drugs, establishing and maintaining excellent pediatric drug development programs can be driven to some extent by higher income medicines.”²⁴

Congress has also recognized the relationship between the incentive and development of pediatric research infrastructure. “The [Senate HELP] Committee is aware that the incentives created by the pediatric exclusivity provision have encouraged the drug industry to develop and expand its infrastructure and expertise in the study of drugs in pediatrics.”²⁵

The pediatric exclusivity incentive must be preserved to ensure that pediatric drug development is not hindered in the face of uncertainty over likelihood of reauthorization and rising research costs. Diminishing or otherwise reducing the value of the incentive, for instance by reducing the exclusivity period or by tiering exclusivity for certain drug products could also create unintended ripple effects across the entire program. While

²² S. Rep. No. 107-79 (October 4, 2001).

²³ Id.

²⁴ Id.

²⁵ Id.

some have argued the returns received from some products (namely blockbuster drugs) as a result of pediatric exclusivity are not in line with the cost of the studies undertaken, the fact is that blockbuster drugs have created the ability for companies to invest in pediatric programs and infrastructure necessary to conduct research across a company's portfolio. Specifically on the issue of proposals to institute a tiered exclusivity incentive, this structure fails to recognize the basic structure of the pharmaceutical research sector, in which a few high-selling medicines often support the research investment in medicines that are needed but that do not achieve large sales. In fact, research conducted by economists at Duke University found that on average, 7 out of every 10 approved medicines do not recover their average development cost. The authors concluded that companies must rely on a limited number of highly successful products to finance their continuing R&D.²⁶

5. **BPCA and PREA are Complimentary Programs that Should Remain Connected**

BPCA and PREA are complimentary programs that should remain connected. PhRMA would propose eliminating the sunset for both programs or alternatively sunsetting them at the same time. It could be very damaging to the operation of companies pediatric research programs if one program continues without the other. As discussed previously, the pediatric exclusivity provisions have been an overwhelming success, generating more than 120 new pieces of information in drug labeling. At the same time, the pediatric assessment provisions in section 505B of the Federal Food, Drug, and Cosmetic Act have generated new labeling in 40 drug products since

²⁶ Grabowski H. and Vernon J., "Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics, Vol. 13, 1994.

enactment of the legislation in 2003, according to the FDA.²⁷ Together, these two programs have worked extremely well to generate new information on pediatric uses of drug products, and they should remain linked. In the past, Congress made certain that the PREA study authority remained in effect so long as the pediatric exclusivity incentives also remain in effect. This ensured that the two programs were tied together, and evaluated together. This is the right approach. Given the success of the programs and the complimentary nature of each to the other, there is simply no reason why the two programs should be de-linked. Accordingly, we urge Congress to adopt a mechanism that allows both to be both made permanent or both re-examined in 2012.

PhRMA strongly urges Congress to reauthorize the BPCA and PREA without modification. The increasing rate of industry study proposals and written requests for studies by FDA shows continuing progress, which would be significantly undermined if this important legislation were allowed to expire. In addition, we urge Congress to proceed with caution when considering changes to the incentive that could have unintended consequences to pediatric research.

F. Conclusion

Since its enactment in 1992, PDUFA has brought about tangible benefits to patients, the FDA, and the pharmaceutical industry. FDA's appropriated resources have been augmented by industry user fees, providing the Agency with sufficient

²⁷ Statement of Rear Admiral Sandra Lynn Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, "Programs Affecting Safety and Innovation in Pediatric Therapies," May 22, 2007.

resources to conduct reviews of new pharmaceuticals in a thorough and timely manner assuring widespread patient access.

The FDA's PDUFA-IV proposal is no exception to this approach, and contains important new provisions and resources to:

- enhance and modernize the FDA drug safety program,
- add a new user fee program to give FDA additional resources to review and provide advisory opinions on direct to consumer television advertisements,
- improve drug development, and
- provide more stable financing for the program.

PhRMA supports FDA's PDUFA-IV proposal, and urges Congress to reauthorize it as rapidly as possible.

The current drug safety system is robust and effective, ensuring that drugs are rigorously tested before they are marketed and closely monitored after approval for any emerging safety signals that need to be factored into the benefit-risk equation. But there is no question that even a good system can be made better. Despite its critical role in monitoring drug safety and protecting the public health, FDA has been chronically underfunded for many years. FDA's most pressing needs, therefore, are for resources to fund its postmarket surveillance activities and a more modernized approach to drug safety that leverages new techniques and resources.

PhRMA believes that the robust drug safety provisions in the PDUFA-IV proposal address all of FDA's drug safety needs. These new provisions, along with FDA's own internal reforms, should be allowed to work to enhance and modernize the drug safety system. We are concerned that adding significant new authorities and a

markedly different review paradigm such as the REMS, may actually be counter-productive. The REMS process creates a complicated and bureaucratic safety oversight system that may not be workable in practice. These additional processes may actually impair drug safety oversight by miring FDA safety officers in unproductive bureaucratic exercises rather than meaningful safety surveillance activities. At the very least, such processes (and hence resources) should be focused on drugs with significant risks, rather than being applied to all products.

If Congress believes that the drug safety enhancements in the PDUFA-IV proposal are not sufficient and that FDA needs additional authorities, this should be accomplished through carefully targeted revisions to the FDCA. For example, an accelerated label revision process could be added to the Act to ensure that labeling discussions on important safety issues do not extend too long. Significantly, this change and other targeted revisions can be accomplished *without* creating an entirely new bureaucratic maze.

Finally, BPCA, combined with PREA, have been pivotal in creating a positive, sustainable environment for pediatric drug research in the US. The impact of BPCA has been undeniable, with over 128 products labeled with pediatric indications since the start of the program. Given this evidence base, Congress should carefully consider the implications of changing the already-proven structure of these programs before making changes. Particularly, the introduction of exclusivity tiering or exclusivity adjustment will create significant uncertainty in the program, which in turn may reduce the amount of pediatric research that is undertaken. It is also important that PREA remain connected

to BPCA, as the two are inherently linked. As such, PhRMA would propose eliminating the sunset for both programs or alternatively sunseting them at the same time.

PhRMA wants to work with FDA and all stakeholders to improve key aspects of FDA's programs in a meaningful way that preserves innovation and patient access. We believe that significant strides already have been made with the PDUFA-IV proposal, particularly with regard to drug safety, and we ask you to reauthorize PDUFA-IV as quickly as possible. We also urge Congress to focus on targeted drug safety reforms to address key issues with the existing robust systems, as well as to reauthorize BPCA and PREA as currently authorized.