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Congress of the United States
House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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December 17, 2013

Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock:

Thank you for appearing before the Subcommittee on Health on Friday, November 15, 2013, to testify at the hearing entitled "Reviewing FDA's Implementation of FDASIA."

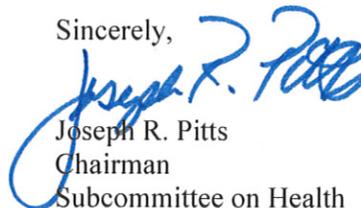
Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests by the close of business on Thursday, January 9, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Attachment 1—Additional Questions for the Record

The Honorable Joseph R. Pitts

1. Congress enacted Title VIII of FDASIA, entitled “Generating Antibiotic Incentives Now (GAIN)”, to provide incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life threatening infections. Under GAIN, a drug may be designated as a qualified infectious disease product (QIDP) if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review. According to section 505E(d)(1), the Secretary shall, not later than 60 days after the submission of a QIDP designation request, determine whether the drug is a qualified infectious disease product. The Committee understands that the Agency has not met the 60-day deadline on a number of submissions for QIDP designation.
2. Is there presently a backlog of pending QIDP submissions at the Agency? What percent of QIDP designations has the Agency acted on timely? As of September 30, 2013, how many sponsor submissions for QIDP designation were beyond the 60-day review period? And how many determinations, if any, has the Agency made since October 16, 2013? Is there presently a legal or policy issue under review within the Agency regarding QIDP designations?
3. Congress is concerned that certain agency interpretations of the GAIN Act may inadvertently limit the development incentives Congress enacted. For example, we have heard that the agency may be designating QIDP status for a drug in a specific indication, rather than for a drug itself, and that the provisions of 21 U.S.C. 355f(c) “Limitations” may be interpreted in a way that renders 5-year exclusivity extension unavailable if a sponsor initially seeks approval for a different indication. Requiring a particular sequencing of indications creates hurdles that could reduce the incentives to develop the drug, even once a drug has received QIDP status and therefore has been deemed to be intended to treat serious or life threatening conditions. Please explain how FDA has interpreted the statutory exclusivity to apply if a drug receives QIDP designation, but then receives a first NDA approval for a different indication than the one described in the QIDP application.
4. Does FDA interpret 21 U.S.C. 360n-1 and 356(a)(1) (as amended by the GAIN Act) to require the Agency to mandatorily apply fast track and priority review procedures, or only if an application for a product with QIDP status requests these review timelines and procedures? Does FDA regard this issue as impacting the availability of exclusivity in any way?
5. To further oversight and reassessment of QIDP incentives within 5 years after the enactment of GAIN, the Secretary of Health and Human Services must submit certain program information to the House Energy and Commerce and Senate HELP Committees, including, for example, a list of qualified infectious disease products and information on the types of exclusivity granted for each product, along with other product information. Does FDA intend to limit the disclosed information in accordance with existing protections of the Freedom of Information Act and other applicable laws? For example, will information about unapproved applications be disclosed or protected from disclosure?
6. The Committee would like to thank the FDA for its outstanding work to address the public health crisis of unintentional overdoses of acetaminophen. Recognizing the high incidence of liver damage due to acetaminophen overdosing, the Agency has responded with a variety of measures to improve safety, including developing education programs and improving the labeling of acetaminophen-containing products. However, one aspect of the Agency’s response still concerns

me and that is the removal of prescription combination products containing acetaminophen in quantities greater than 325 mg by January 14, 2014.

So that we can continue to protect the health of U.S. citizens from the unintentional overdoses of acetaminophen, please provide a response to the following questions:

- a. What are the plans of the FDA to enforce the January 14, 2014, deadline and ensure that no prescription products containing no more than 325 mg of acetaminophen remain on the market after that date?
 - b. Does the FDA intend to do a full and total recall on January 14, 2014, including one that has pharmacies removing these products from inventory for sale? If not, what steps is the FDA taking today to ensure that manufacturers have stopped production, distributors have slowed distribution, wholesalers have scaled back inventory, and pharmacies are allowing current stock of the high dose products to run out and are prepared to transition to the new products on January 14, 2014?
 - c. If a full and total recall on January 14, 2014, is not the intention of the FDA, are you going to share with the industry and the public the rationale for that decision, in light of the safety concerns that prompted the original request in January 2011?
 - d. Does the FDA have an early indication of whether all pharmaceutical manufacturers intend to meet the FDA's request that all prescription products with more than 325 mg of acetaminophen be withdrawn from the market by January 14, 2014?
7. How does the FDA work with DEA after they have reviewed an application and made a scheduling recommendation? Is the DEAs scheduling review process incorporated into the PDUFA timeline? What could be done to improve the DEA scheduling process from the FDA's perspective?
 8. One of the anecdotes we hear from industry and investors, and the data seem to support, is that for certain therapeutic areas, such as oncology, the FDA has an exceptional track record of rigorous but efficient and timely review process, but for others it is long and drawn out. FDASIA requires some very basic review-level data and provides an opportunity for further analysis to enhance our understanding by looking at review times and other metrics by review division. Recognizing differences in science and disease understanding, what are you doing to replicate some of the best practices in your strongest review divisions across the agency?
 9. In your testimony, you note that you are making significant progress in implementing FDASIA and meeting most due dates. Which due dates are you missing and when does the Agency plan on completing them?
 10. Since GDUFA does not provide review of predictability or metrics for backlog ANDAs or for ANDAs submitted during the first two years of GDUFA it is difficult to quantify the work the Agency has been doing. What has the FDA done to improve communication with industry in order for manufacturers to be able to predict when the FDA might take action on these applications?
 11. Of the 234 new hires under GDUFA, will you breakdown approximately how many hires were on-board in each of Q1, Q2, Q3 and Q4 of FY 2013? Are all 234 new hires actually on-board today?

New hires is an important foundational goal of GDUFA, and actually one of the only goals for FY 2013 and FY 2014. Will you further explain why it took so long for the FDA to actually hire and on-board the 234 FTE's?

12. We recognize training is vital for new hires. Approximately how long does it take a new FDA employee to become a fully productive ANDA reviewer or facility inspector?
13. Given the backlog of pending ANDAs and facility inspections (the tenets or principles on which GDUFA was negotiated, legislated and implemented), will you give the Committee an estimate on how many of these new hires are scientists dedicated to ANDA review? How many are to be facility inspections? And of the remaining 234 not accounted for in these two principle job functions, what job functions will they be providing related to GDUFA?
14. For FY14, you have a goal of approximately 465 new hires. Please provide the breakdown by Quarter in FY14 for on-boarding these new hires and the functional areas they are to be assigned.

Despite the slow start, I commend the FDA for being able to fill so many positions in the latter half of FY13. Does the rapid hiring at the end of FY13 mean that the FDA now has a well-established hiring process for the GDUFA program and will be able to meet this hiring goal earlier in the year for FY14? For example, it is my understanding that GDUFA is estimated to support the hiring of about 900 new FDA employees by the end of FY15. How many of those new hires will be dedicated to actual technical review of pending ANDAs and inspectional review of facilities, as opposed to administrative functions within CDER?

15. Over the past several years, the U.S. Food and Drug Administration (FDA) has been tasked with the evaluation and the weighing of the appropriate use of opioid analgesic drug products. For the millions of American patients experiencing an acute medical need or living with chronic pain, opioids, when prescribed appropriately, can allow patients to manage their pain as well as significantly improve their quality of life.

At the same time, this Committee has become increasingly concerned about the abuse and misuse of opioid products, which have reached epidemic proportions in certain parts of the United States. The value of, and access to, these drugs for patients in pain is unquestioned. My concern is that the FDA has yet to establish nor has yet determined how to balance the need to ensure continued access to those patients who rely on continuous pain relief while addressing the ongoing concerns about abuse and misuse.

Abuse Deterrent Formulations (ADFs) for scheduled narcotics show significant promise to reduce prescription drug abuse. While not yet perfect, even the FDA has recognized that the ADF technology as applied to the recently approved reformulation of OxyContin is a significant step in protecting patient's access while curbing abuse of this powerful opioid.

With the forgoing in mind:

- a. When does the agency expects to finalize its draft labeling guidance?
- b. Will you consider the approach outlined in the draft labeling guidance to be equally applicable to products other than opioids?
- c. Does FDA believe that it has sufficient existing authority to incentivize development of abuse deterrent products?

- d. If so, will the FDA utilize all of its existing authorities to create incentives for such products?
 - e. Why did the FDA approve a new product, Zohydro, without requiring an ADF in the formulation? Can Zohydro in its approved form be crushed and snorted or crushed diluted and injected?
 - f. Does the FDA believe that there will be an expanded use of ADFs without an Agency mandate to include such formulations in new NDAs/ANDAs?
16. In January, the FDA issued a draft guidance for industry on development and labeling for abuse-deterrent formulation (“ADF”) products. Although the draft guidance lists the basic concepts of FDA’s perspective on ADFs, from technology manufacturers the paper lacks both clarity and detail necessary to support the development and broad application of ADF technology for abused products. For example,
- a. Some of the references and examples made in the guidance are applicable to only a subset of technology approaches and not relevant to others.
 - b. There is no detailed guidance on differential requirements for immediate release opioids and combination products.
 - c. A perspective on how to address newly introduced ADF products that do not have a non-ADF predecessor version or reference product is missing.
 - d. Last, there is not any structured guidance on how FDA is going to assess ANDA applications in the context of the guidance requirements.

Although technology developers and manufacturers started developing ADF technologies more than ten years ago, the FDA claims that the science of abuse deterrent formulation assessment is new and requires case-by-case assessment. This position lacks the clarity and reliability necessary for companies that require continuous funding and investment for their technology development.

Will you give this Committee a specific date by when the FDA will finalize the guidance for ADF development labeling, including addressing the missing pieces I just mentioned?

17. Do you believe that FDA is lacking legislative authority to reject approval for non-ADF extended release opioid products?
18. Does the FDA believe it should be able to continually progress the opioid market into one where all opioids will have to have ADF technology to protect and minimize misuse and abuse?
19. How is interagency development of REMS for controlled substances coordinated? For example, how is DEA brought in to ensure that a REMS will not conflict with DEA’s regulations? Does FDA consult with SAMHSA and/or the HHS-Office of Civil Rights on REMS compliance with HIPAA and other privacy laws regarding information about controlled substances? Finally, how is it ensured that controlled substance REMS do not put pharmacists in the untenable position where compliance with a REMS would require violating state controlled substance or state pharmacy laws?

20. With recent reports of hackers gaining access to DCER's on-line submission systems compromising the information of approximately 14,000 current and past users, how has the FDA responded to this and similar attacks and what has been communicated to stakeholders?
- What is the Agency's enterprise-wide plan to ensure the security of electronic submissions, confidential patient information, and reporting systems?
 - How will stakeholders be assured of the Agency's ability to fulfill their legal obligation to protect the confidential commercial information that the Agency receives on a daily basis?
21. As part of the PDUFA V Goals Letter and related requirements under FDASIA, the goals and the statute provide implementation of a number of critical electronic submission and data standardization goals and requirements. As such, the FDA is required to public a strategic plan detailing how these goals and requirements will be implemented. Given that the last available PDUFA IT plan was published in September 2011 with information current as of May 2010, what is the status of the PDUFA IT plan?
- Will the plan include a strategy for the support, maintenance and security of critical, foundational systems, such as the Electronic Submissions Gateway, that are central to the FDA's ability to receive and process the electronic submissions that will be required of sponsors per Section 1135 of FDASIA?
22. I understand that the Agency utilized emergency funds to continue operations in response to sequestration. What is the current status of these emergency funds?
23. Please provide the Agency's Social Media budget and strategy plan to the Committee.
24. It has been the agency's policy and practice that in vivo (human) clinical testing is required to establish bioequivalence for most locally acting topical drugs. What scientific determination did FDA make to justify its departure from this prior policy and practice when it issued its new draft bioequivalence guidance for cyclosporine ophthalmic emulsions?
25. FDA has stated that they will engage stakeholders in the process to facilitate treatments for those with serious and life-threatening illnesses particularly where there are little to no treatments available.
- How are you engaging the pharmaceutical industry in this process? Specifically, what steps has the FDA taken to engage with the ME/CFS community and innovators with expertise in this area?
 - Under the new patient focused drug development meetings, what role do the drug innovators play?
 - How exactly is FDA engaging with innovators on these unmet medical needs? Are you examining treatments currently in the pipeline?
26. The Federal Food, Drug, and Cosmetic Act (Act) stipulates that the critical distinction between a drug and a medical device is that a medical device "does not achieve its primary intended purpose through chemical action within or on the body of man." The plain language of the Act indicates that a device may have more than one primary intended purpose. In 2011, however, FDA issued a draft guidance titled "Classification of Products as Drugs and Devices & Additional Product Classification Issues" indicating that if a product has "multiple therapeutic effects," each would

be considered a “primary intended purpose.” By designating all purposes as primary, this statement appears to be inconsistent with the plain language of the Act. The draft guidance also states that if any of these intended purposes were achieved through a chemical action within or on the body of a man, the product would not meet the definition of a medical device. This change in policy has resulted in products that would have been historically regulated in the U.S. as devices being regulated as devices in the rest of the world, but regulated as drugs in the United States. I have several questions regarding this draft guidance and how FDA is classifying medical devices:

- a. Given that there are numerous products classified as devices that have some chemical action within or on the body of man, would you agree that the draft guidance reflects a substantial policy change by requiring a product to be classified as a drug if any of its intended purposes are achieved through a chemical action within or on the body of a man?
- b. Would you agree that similar products should be regulated in the same manner and that the substantial policy change could have an impact on new products being regulated similarly to products on the market prior to issuance of the draft guidance?
- c. The plain language of the Act indicates that a device may have more than one primary purpose. The 2011 FDA draft guidance appears to arbitrarily depart from this plain language. What is the rationale for doing so?
- d. This draft guidance has not been finalized but appears to have been implemented by FDA. Would you agree that a draft guidance document should not be implemented until final?
- e. The FDA recently applied its revised interpretation of the Act set out in the 2011 draft guidance to classify a portable body shower as a drug rather than a medical device. The U.S. District Court for the District of Columbia found that the FDA designation of the product as a drug was based on a “doubly grandiose” interpretation of the phrase “primary intended purpose.” When and how will FDA revise the 2011 draft guidance to reflect the ruling?
- f. Despite the court ruling, FDA has persisted in its determination that the portable body shower be classified as a drug. In response to the ruling, FDA created a new “meaningful contribution” standard for determining if a product is a device. Please explain how FDA developed its “meaningful contribution” test and what criteria FDA will apply in determining whether that test is met. How is it that FDA can reinterpret statute seemingly at will?
- g. What impact will such draft guidance and the new “meaningful contribution” test have on regulatory predictability? How can manufacturers be sure guidance will not be further revised without their input?
- h. How do you propose we use reasonable efforts to harmonize its classification of products as drugs and medical devices with other global regulatory agencies?
- i. Could requiring companies to comply with US drug regulations, when they are required to comply with medical devices regulations in all other countries for the identical product, place an unreasonable burden on the companies and could prevent introduction of important products to U.S. patients?

27. Has the agency taken any specific action to promote the development of treatments related to Duchenne Muscular Dystrophy? Specifically, has the agency considered using its accelerated approval process authority in FDASIA to promote the development of Duchenne Muscular Dystrophy given the challenges of designing and populating a Phase III clinical trial with these patients? What successes, challenges and setbacks has the agency encountered in this area?

The Honorable Frank Pallone, Jr.

1. How much has the biosimilars program received in user fees in FY13 and FY14 to date?
2. For FY2013, the FDA committed to find the \$20 million “trigger” monies from within their FY2013 appropriations if additional monies were not appropriated by Congress for biosimilars. Has that occurred?
3. What is FDA’s commitment for 2014, and subsequent years through 2017?

The Honorable Marsha Blackburn

1. FDA’s draft bioequivalence guidance for cyclosporine ophthalmic emulsions has been questioned by patient and provider groups, such as the American Academy of Ophthalmology, the American Glaucoma Society, the American Society of Cataract and Refractive Surgery, and the American Optometric Association. As health and safety concerns have been raised, does the agency plan to publicly withdraw the draft guidance and reconsider the matter?
2. How much the agency collected in user fees for the biosimilars user fee program in FY2013 and how much is has collected thus far in this fiscal year?
3. How many Special Protocol Assessment (SPA) agreements has the review division and/or FDA interpreted to be no longer binding due to failure of a sponsor to follow a protocol agreed upon with the Agency?
4. How many SPA agreements has the review division and/or Agency found to be no longer binding based on false statements, misstatements, or the omission of relevant facts?
5. How frequently does the review division and/or Agency agree to modify a SPA?
6. How many SPA agreements has the review division and/or Agency rescinded based on review division and/or Agency determination that a substantial scientific issue essential to determining the safety or efficacy of the drug has been identified after the testing has begun?
7. One of the goals of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act was to spur innovation in treatments for children with rare diseases, and specifically for children with cancer. I would like to ask you whether you believe this legislation has been successful for children battling Pediatric Low-Grade Astrocytoma (PLGA) and other rare pediatric cancers. Pediatric Low-Grade Astrocytoma is a slow growing children’s brain cancer that impacts over 20,000 children in the United States. Each year, over 1,000 new children are diagnosed with some type of astrocytoma brain tumor. The treatment options currently available to children with slow-growing PLGA brain tumors are invasive, highly toxic and ineffective.

Some pharmaceuticals that are effective in treating adult cancers are being examined to treat PLGA brain tumors. For example, a drug that is approved for treatment of primary kidney cancer and advanced primary liver cancer is being examined for treatment of PLGA. With funding from the PLGA Foundation and the Making Headway Foundation’s Talbot Family Research Fund, a phase II clinical trial of this drug for the treatment of children and young adults with recurrent or

progressive Low-Grade Astrocytoma has opened. These are the kinds of research synergies and laboratory collaborations that hold promise for significant breakthroughs and give hope to children with PLGA and their families.

Are the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) helping to incentivize these types of research synergies for rare children's cancers like PLGA? Are there other barriers that exist to advancing new clinical trials for PLGA that Congress should be examining?

The Honorable Gene Green

1. Section 575 of the FDA Safety and Innovation Act allows the FDA to designate new medical gases after "taking into account any investigational new drug application...for the same medical gas submitted" under certain conditions. This is a very broad power to be exercised by the Secretary of the Department of Health and Human Services. Once designated, the gas and its use would be immediately generic and available for use by all companies, undermining the significant financial and resource investments made by companies or universities in bringing new medical gases to market. These entities typically have the legal protections provided to the medical drug industry for intellectual property related to INDs. But, this power, if exercised, would eliminate those protections.

I understand that the FDA declined to address this important issue in its "Guidance for Industry: Certification Process for Designated Medical Gases," stating: "This document does not discuss how FDA plans to implement its new authority to designate gases..."

Moreover, in a written response to Members of this Subcommittee inquiring about this issue, the FDA acknowledged that these concerns are real and that the exercise of this authority could "lead to losses for the persons or entities that have invested resources in that IND...and could disincentiveize others from pursuing IND...applications for new medical gases in the future." Yet the response also leaves ample room for FDA to exercise its authority and do just that.

Will you assure Congress that the FDA does not intend to undermine pending and legitimate INDs by listing the medical gas in question under its section 575 (H) authority? Upon finding a pending and legitimate IND, will you allow the IND process to proceed normally, enabling an entity to bring the medical gas to market, protect its research and realize its investment?

The Honorable Michael C. Burgess

1. It is my understanding that early clinical trials for many rare diseases are only being conducted outside the United States. Many times, the challenge is differences in how the flexibility in international guidelines are applied in the U.S. for first in human studies. How can the FDA improve its flexibility to ensure that U.S. patients have access to these potentially lifesaving clinical trials?
2. What is the FDA assessment to date of the impact of Breakthrough therapy designation to expedite the availability of life-saving medicines to patients? Given that many more breakthrough therapy designations have been granted than was anticipated—has this had an impact on the availability of resources for each designation (i.e. are they able to actually spend as much additional time on each as they had intended)? Has the high number of designations led to a prioritization of certain products with the designation over others with the designation?
3. What is the FDA assessment to date of the impact of "The Program" for NMEs and Original BLAs to expedite the availability of life-saving medicines to patients?

4. What is the FDA assessment to date of the impact of the Patient-Centered Drug Development goals in the FDA performance goals and other patient-centered components of FDASIA?
5. I am concerned about the recent FDA decision to recommend hydrocodone combination products. Patient access continues to be a concern for patients, as well as physicians if hydrocodone-containing medications are indeed rescheduled.
 - a. The FDA has made its recommendation to reschedule these medications. However, the agencies' report justifying your recent decision has not been made public. When will this report be sent to HHS? When will this report be made public?
 - b. I am not aware that the FDA has access to new scientific research showing that rescheduling would address prescription drug abuse and diversion of these drugs. Will you provide us with any new information on any new scientific data FDA has that suggests rescheduling these products will substantially curb misuse and abuse?
 - c. Will you provide us with any new scientific data the agency has that addresses the potential impact rescheduling will have on patient access to these medications?
 - d. How can the FDA prevent the rescheduling from having a negative impact on patients in nursing homes who need opioid analgesics?
 - e. Let's take the example of a hospital lab, which might be involved in basic research, clinical trials and patient testing. How would a manufacturer know with any precision what the hospital is using these instruments for? Should the hospital have to buy multiple machines to keep a firewall between different users? Should the manufacturer cut off legitimate business opportunities just in case there is a theoretical possibility of clinical use?
6. In April, you determined that OxyContin was an abuse deterrent formulation. You later made a determination that Opana reformulation did not meet your standard. Then you recently approved Zohydro, an extended release ER single entity hydrocodone with no abuse deterrent products and that industry, both innovator and generic, need to have a clear understanding of FDA's standard. I am concerned that the current regulatory requirements are so confusing that innovators may just walk away from developing abuse deterrent formulations. When you approve non-deterrent products it seems like a step backwards. Will you provide more detail on the standard that is being applied by the FDA in this realm?
7. Section 901 of the FDA Modernization Act of 1997 (FDAMA) as amended by the FDA Safety and Innovation Act (FDASIA) creates a clear pathway for treatments for rare diseases to receive accelerated approval. The first criteria is that the disease be rare and life threatening. As you know, Duchenne Muscular Dystrophy affects approximately one in every 3,500 boys and is always fatal. In your view, does Duchenne meet this criteria?
8. FDASIA requires safety data be carefully weighed in a risk vs. benefit analysis, taking into account the needs and viewpoints of patients. In a case where a drug treats a rare and life threatening disease plus shows no adverse events and has no measurable or unanticipated negative side effects, would you please explain in detail how the FDA would take into consideration this safety profile and the views of patients and families regarding risk and benefit?

The Honorable Phil Gingrey

1. On June 12, 2013, in the Federal Register, FDA published a proposed rule titled “Establishing a List of Qualifying Pathogens under the Food and Drug Administration Safety and Innovation Act.” In section C of the Proposed Rule, the Agency states that “...inclusion of a pathogen on the list of ‘qualifying pathogens’ does not determine whether a drug proposed to treat an infection caused by that pathogen will be given QIDP designation.” In the same section of the Proposed Rule, the Agency further states “...the development of a treatment for an infection caused by the pathogen included in the list of ‘qualifying pathogens’ is neither a necessary nor a sufficient condition for obtaining QIDP designation...” In essence, does the Agency consider the list as having any real bearing to qualified infectious disease product (QIDP) designation?
2. 21 USC 355E(g) provides the definition of QIDP: “The term ‘qualified infectious disease product’ means an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by—(1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens; or (2) qualifying pathogens listed by the Secretary under subsection (f).” Participants in the legislative process greatly debated this definition, predominantly because the term “serious or life-threatening” is not defined in statute, only in guidance, and therefore could be modified in the future. On the other hand, the statute not only defined “qualifying pathogens,” it also set up an elaborate and formal process for determining pathogens that can make the “qualifying pathogen” list. Thus, by stating that “serious or life-threatening infections” include those caused by “qualifying pathogens,” Title VIII of FDASIA provided some certainty and transparency early in the clinical development process about which products could be eligible for QIDP designation. If the Agency’s proposed interpretation of the statute stands, would not the intended certainty or transparency be lost, and the “qualifying pathogen” list would serve no real purpose and carry no weight whatsoever, making it inconsistent with the intent of Congress?
3. Since clinical data is usually limited on resistant infections and generic companies are not about to conduct new clinical trials for old drugs, isn’t it critical that FDA also use all the tools at its disposal to set and update breakpoints, tools like pharmaco-metric and pharmaco-dynamic data (PK PD), nonclinical data, and state-of-art statistical methods to both update old breakpoints and as well as to set new breakpoints for products before the FDA for approval?
4. The 2012 GAO report found that the Agency was way behind in updating breakpoints. Will you provide the Committee with an update? How many marketed antibiotics are there in the U.S. for which the breakpoint for the product label has neither been confirmed nor updated? What is the agency’s plan for getting this done as well as what is FDA’s process and plans to update breakpoints moving forward?
5. The 2012 GAO report found that FDA had not taken any regulatory action against companies that failed to respond to the agency’s efforts to obtain updated breakpoint information. Has the FDA taken any regulatory action against such companies since the publication of the GAO report and if not, why not? What type of regulatory action can the FDA take in this situation?
6. Antibiotic products have a number of challenges in terms of their development that may lead to clinical data not entirely reflective of when a new QIDP candidate may actually work.

In antibiotic development, the least sick individuals tend to be in clinical studies to assure that such patients have NOT been exposed to other antibiotic products before the study product is introduced. This “exclusion criteria” that helps power a pivotal clinical trial may also ironically reduce or even exclude the enrollment of patients with resistant infections.

In other words, a significant amount of potentially relevant clinical data cannot be collected and, therefore, a newly established clinical breakpoint for QIDP product could be inappropriately high. Do you agree that this potential exists, that is setting a new breakpoint too high? How does FDA propose to deal with this situation, whereby the data in clinical studies may be skewed to the least sick patients and then the need for new QIDP product with breakpoints that are not set so high that the sickest do NOT have access to life saving antibiotics?

7. In order to maximize the effectiveness of the GAIN Act, will you clarify that the establishment of breakpoints for such QIDPs would utilize both clinical and additional forms of evidence, as well as rely upon advanced statistical methods as appropriate, to ensure their breakpoints are set appropriately and, importantly, not set too high especially in light of the unique circumstances confronting QIPD product development already outlined?
8. What steps is the FDA now taking to assure that breakpoints for new QIDPs rely on these other sources of non-clinical data and what has been industry's response?
9. Advisory Committee decisions are not binding on the FDA, but three years ago, the Anti-Infective Drugs Advisory Committee decided that "It would not be the best use of resources for FDA to duplicate the work CLSI when, essentially, the same experts would be utilized...[and] One suggestion was that the Agency should have a working group to routinely evaluate published and unpublished data for each drug class...If interpretation of the data differs among FDA and CLSI, it should be brought before the [Advisory] Committee."

Would it not be appropriate for FDA to rely on such outside expert findings with regard to breakpoints? And isn't it actual practice now for physicians and other health care providers to rely on CLSI and other expert third party breakpoint findings because this information is more up to date and reflective of scientific knowledge than what's on the FDA label for many antibiotic products?

10. The growing resistance of several bacterial strains to all or nearly all antibiotics currently approved is a public health emergency. Recently, the Centers for Disease Control and Prevention (CDC) issued an alarming report on this topic, noting that each year at least 2 million Americans acquire a serious infection resistant to one or more antibiotics designed to treat that infection. CDC warned if we do not take steps now, we could be entering a "post antibiotic era."

The FDA has indicated that it agrees that product innovation is one of the keys to solving this situation. In addition to the GAIN Act, what other specific incentives might work to significantly grow antibiotic innovation?

11. Just recently FDA released a proposed rule that would fundamentally change the way that doctors and pharmacists access and interpret drug labelling. Under the proposed rule, at any given time there can be multiple labels for a single medication. The FDA acknowledges that 1) the purpose of drug labeling is to inform prescriber decisions about the benefit and risk of medicines and 2) that health care practitioners are unlikely to review all of the product labeling, so a website is needed to view proposed but yet to be reviewed labeling changes.

Aren't we creating a situation of great uncertainty for doctors and pharmacists? How will they know whether a proposed change is valid and if this information should be conveyed to patients? How does the FDA expect doctors to view these proposals, as valid changes before FDA has examined them or as mere proposals that have no validity until approved?

Furthermore, this seems to create a new burden to search a website every time the doctor wishes to prescribe a drug to see if any new label has been suggested. Given that doctors currently do not

review these labels regularly, how will you ensure that doctors will review the site for the most recent information?

12. As part of the 2012 MDUFA Goals letter, FDA agreed to new performance metrics for 510(k) and CLIA Waiver dual submissions. An important part of the commitment letter that FDA signed with industry is the issuance of a Guidance by FDA that will help industry understand the requirements of successfully completing dual 510(k) and CLIA waiver applications.

These two provisions will aid the public health through quicker review times and potentially more tests available to doctors and patients. A number of rapid tests for diseases listed in the CDC's recent report on antibiotic resistant pathogens are either in the review process or are nearing the point of submission.

We understand FDA believes this Guidance will be delayed because of issues related to the information technology required for its application tracking system. What are those issues and why would this delay the issuance of a Guidance designed to facilitate the overall management of these applications? As part of dual submissions with a 510(k) application, can CLIA waivers be tracked manually if 510(k)s are tracked electronically? What are FDA's plans to meet the obligations of this FDA/industry agreement if Guidance is not issued?

The Honorable Leonard Lance

1. To be in compliance with FDASIA, the FDA must allow for novel approaches to use pathophysiologic and pharmacologic evidence to support the use of a biomarker endpoint when the low prevalence of disease makes the existence of other types of data impractical to collect. What kinds of novel approaches is the FDA planning to take to allow for the use of surrogate endpoints in clinical trials for rare diseases?
2. How will the FDA ensure the upcoming FDA Rare Disease meeting in January will improve the regulatory process for rare disease, when the FDA held a similar meeting in 2010 and issued a report with recommendations, but has yet to implement any of the recommendations more than three years later?
3. As you may be aware, I have authored legislation, the FDA Safety Over Sequestration (FDA SOS) Act, which would protect the FDA user fees from the threat of sequester, should Congress face a similar budget situation as we did earlier this year. This legislation is supported by many of my colleagues on this committee on both sides of the aisle and it is our hope that it be considered and passed soon in order to maintain predictability in the review process, as well as incentive to continue to engage in these agreements.

OMB unfortunately interpreted sequestration to apply equally to both FDA appropriations and industry user fees. As a result, more than \$80 million in private user fee funding is being sequestered in an agency account where they cannot be spent or put to any practical purpose. The FDA Safety Over Sequestration (FDA SOS) Act would clarify that industry user fees cannot be sequestered. From the perspective of a senior FDA manager, what impacts is the sequestration of user fees having on FDA operations, regulatory science, and product evaluation? Would you support passage of the FDA SOS bill?

4. Briefly, how are Agency operations impacted by sequestration? As a result, how are you absorbing these cuts?
5. How has sequestration affected product review times, if at all? Are certain products/review divisions/therapeutic areas more or less impacted than others?

How has sequestration, including of industry-paid user fees, impacted the Agency's ability to implement FDASIA in terms of the new responsibilities it is required to undertake with respect to promoting innovation, stakeholder engagement, and drug supply chain integrity?

6. It seems that the decision to sequester the PDUFA user fees violates the intent of the statute that the industry's user fees should only be used for the review of new medicines. Has the agency discussed any strategy to release the sequestered fees through the FY2014 fiscal process or otherwise?

Have you talked to either the House or Senate Appropriations Committees about finding a mechanism to release the fees? Has FDA requested that HHS or OMB release the fees? When and who took part in these discussions?

Has FDA questioned OMB's analysis that PDUFA user fees are subject to sequester or any other use than for FDA's human drug review program? If so, when did FDA have these discussions and with whom?

7. FDA continues to be unable to access approximately \$83 million in sequestered user fees for FY2013. The loss of these fees has meant that the implementation of key aspects of FDASIA have been delayed including the hiring of any new scientific and medical personnel to advance crucial regulatory science priorities. Undoubtedly, this is bad for patients, bad for science and bad for public health.

Given the gravity of the impact losing these fees has had on the agency's ability to fulfill its public health mission, shouldn't a mechanism to release them be among the Agency's top priorities for anomalies in any end of year fiscal package? Has the agency communicated with the Hill about such an anomaly? If so, to whom and when?

8. Budget and Appropriations leaders have indicated that giving "flexibility" to agencies in how sequester cuts are implemented is a top priority for the end of year fiscal package. What kind of authority would FDA need for there to be a real impact on how effectively the agency is able to mitigate the impact of the sequester, including user fee programs? Have you communicated this to Budget and Appropriations negotiators by providing them with language or engaging in any conversations at all?
9. As you know, FDASIA included bipartisan language that I advanced with the help of your staff at FDA to resolve a 100-year old issue and create a pathway for medical gases to become approved drugs. I am proud that New Jersey is the home of numerous health care companies that manufacture medical gases used by millions of patients around the country. I am very eager to see the full implementation of these medical gas provisions.

For instance, FDASIA requires that FDA update its current regulations to take into account the unique characteristics of medical gases. FDA is required to report to Congress on the proposed changes in January 2014 and complete all changes by July 2016. FDA's current regulations have caused enforcement issues for decades both for FDA as the regulator and for the regulated community, including expiration dating and calculation of yield. These are issues that must be resolved through amendments to current regulation, as opposed to guidance, in order to provide certainty. I understand that safety organizations representing our New Jersey manufacturers have submitted extensive comments on the changes that are necessary to the current regulations.

Will you provide me with an update on progress working with stakeholders to update the necessary federal regulations as well as assure this committee that FDA regulations will be updated to incorporate medical gases by the July 2016 deadline?

10. I am pleased to hear that certification of medical gas manufacturers is already underway, however I am concerned there is not yet final guidance in place resolving key issues like documentation for subsequent manufacturers. When can Congress expect to see final guidance on the medical gas certification process?

The Honorable Bill Cassidy

1. In the event a foreign and domestic manufacturer are similar situated, such as in the case when both the foreign and domestic manufacturer would be providing an unapproved drug to mitigate a drug shortage, what criteria does FDA consider and use to determine which manufacturer will be permitted by the Agency to provide an unapproved product to mitigate the shortage?
2. Does the FDA have a standard operating procedure as it relates to evaluating both domestic and foreign manufacturers for their ability to provide drugs unapproved by the FDA in the event of a drug shortage? If so, please provide that operating procedure.
3. In the Strategic Plan for Preventing and Mitigating Drug Shortages report released in October 2013, the FDA briefly mentions the Gray Market but notes that the agency has limited data on the gray market and no authority regarding production pricing. Has the FDA reached out to CMS to collaborate to learn more about the Gray Market and drug pricing in respect to studying the recent jump in drug shortages?
4. FDA plans to provide expedited entry for Secure Supply Chain Pilot participants, but does not clarify how much faster. Will FDA collect data on how the program impacts clearance rates?
5. The Secure Supply Chain Pilot needs to cover a substantial portion of imports in order to enable FDA to focus its resources on high risk imports. Unfortunately, we are hearing from many qualified companies that the program is not compelling. For companies that plan to participate, the program will cover only a sliver of their imports. In terms of participation rates and amount of trade covered, what are FDA's metrics for success for this program? If FDA does not meet those metrics, is it prepared to pivot to a new, meaningful program, or will it allow the pilot to continue with only a few participants?

The Honorable H. Morgan Griffith

1. While the Senate has now passed and the President has signed into law the Drug Quality and Security Act (H.R. 3204), I am still focused on the overwhelming need to protect patient safety and ensure the drugs patients are receiving are sterile and safe. Many patients rely on the availability of compounded medications to treat a variety of conditions. Without these medications, many patients may not be able to receive treatments they need. Recognizing that both contamination and lack of access may pose serious health risks to patients, how does FDA intend to balance these risks and both ensure safe compounded products while maintaining access to products for providers and patients, specifically including access to compounded products for office use?
2. While the DQSA provides clarity on oversight authority for compounding pharmacies, it lacks some much needed clarity on the issue of office use. However, while office use is not mentioned in 503(a), it is expressly permitted under numerous state laws and regulations governing the

practice of pharmacy. Will the FDA defer to a state regulatory agency when such a conflict between federal and state law exists?

3. H.R. 3204 creates a new class of federally-regulated compounding facilities. These “outsourcing facilities,” which will meet the highest possible drug safety standards, will be able to compound a variety of products for physician and patient use. How does the FDA plan to address who is responsible for regulation those entities which are acting like an outsourcing facility but have not voluntarily registered with the agency?
4. Does the agency intend to petition Congress to expand the definition of an outsourcing facility to include those entities and individuals engaged in the compounding and distribution of non-sterile medications?
5. Does the agency intend to petition Congress to change current language of 503 (b) providing for voluntary registration of an outsourcing facility to a mandated registration?
6. Are outsourcing facilities going to be required to follow Current Good Manufacturing Practices (cGMPs) or, as you indicated in your testimony before the Senate HELP Committee, does the agency intend to promulgate or use a different set of standards with which those firms will be expected to comply?
7. Repackaging of drug products by outsourcing facilities was not an activity specifically covered in the Drug Quality and Security Act. Given the stringent safety, sterility, and inspection requirements on these facilities, as well as the strong need for access to repackaged sterile drug products by many physicians and patients, will the FDA allow outsourcing facilities to provide sterile repackaged drug products to physicians for administration to patients in treatment settings?

The Honorable Gus Bilirakis

1. 109 Members of Congress signed onto a letter urging the FDA to improve access to Accelerated Approval for Rare Disease as required by FDASIA. How is the FDA planning to improve the Final Expedited Approval Guidance due in July 2014 to be in compliance with FDASIA?
2. It is our understanding that only 1 of the 13 accelerated approvals you cited during the last six years was for a disease without historic approvals. To be in compliance with FDASIA, the FDA must allow for novel approaches to use pathophysiologic and pharmacologic evidence to support the use of biomarker endpoint when the low prevalence of disease makes the existence of other types of data impractical to collect. What kind of novel approaches is the FDA planning to take to allow for the use of surrogate endpoints in clinical trials for rare diseases?
3. How many treatments were approved with novel biomarkers used for the first time?
 - a. How many were for indications other than cancer and HIV?
 - b. Have any accelerated approvals occurred with a novel marker and a never before treated disease?
 - c. How many new biomarkers did the FDA accept for a first time use in the last five years?
4. What is being done to ensure that FDA reviewers have a scientific understanding of the diseases that they are reviewing?

5. Will you tell the Committee what additional advice or guidance FDA plans on doing in the coming year in order for the industry to better understand the FDA's expectations, and encourage submission of applications for bio-similar products? Additionally, is the Agency currently developing, or does it intend to develop, any guidance with respect to unique non-proprietary names?
6. Section 1121 of the FDASIA requires the Secretary of HHS, acting through FDA, to issue guidance on the advertising of "medical products" on the Internet by July 2014. When will the FDA issue a draft of its guidance?
7. How is the FDA interpreting the term "medical products?" Does it include prescription drugs? Over the counter drugs? Medical devices Veterinary medicines? Other products?
8. Has the FDA been meeting with parties that will be affected by the guidance required under section 1121—such as prospective advertisers, Internet advertising companies, and social media platforms?
9. Does the FDA have adequate resources to issue guidance in this area? The FDA, for many years, has regulated print and television advertising of prescription drugs, for instance, but has not dealt with digital direct-to-consumer regulation until now. Does the FDA have adequate expertise to understand how various Internet company platforms operate technologically?
10. Will the FDA consider the technological limitations and opportunities that the business models of the various Internet companies? Is the FDA approaching its guidance in a technologically neutral way?

The Honorable Renee Ellmers

1. North Carolina is home to thousands of high paying pharmaceutical jobs. We should help find smart ways to make these facilities more competitive. Unfortunately, FDA frequently but unpredictably detains complaint research compounds and active ingredients from highly compliant importers. Section 713 of FDASIA encouraged FDA to address this problem by distinguishing between highly complaint importers and high risk importers, hence the Secure Supply Chain pilot. The application window will close December 31. How have potential applicants reacted to the program? How many have applied? How many do you expect?

Attachment 2—Member Requests for the Record

During the hearing, Members asked you to provide additional information for the record and you indicated that you would provide that information. For your convenience, descriptions of the requested information based on the relevant excerpts from the hearing transcript regarding these requests are provided below.

The Honorable Joseph R. Pitts

1. Please submit the Agency's internal spreadsheet tracking all obligations you have under this FDASIA.