



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUL 31 2015

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the September 19, 2014, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "21st Century Cures: Examining Ways to Combat Antibiotic Resistance." This letter is a response for the record to questions posed by certain Members of the Committee.

If you have further questions, please let us know.

Sincerely,

A handwritten signature in black ink, appearing to read "Thomas A. Kraus", with a long horizontal flourish extending to the right.

Thomas A. Kraus
Associate Commissioner
for Legislation

Enclosure

cc: The Honorable Frank Pallone, Jr.
Ranking Member

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1.1 When considering the importance of antibiotic breakpoints, what barriers do you face when attempting to keep them up to date?

The current system for updating breakpoint information in antimicrobial susceptibility testing (AST) devices is not getting up-to-date information regarding the susceptibility of bacteria and fungi to health care practitioners fast enough. Under the current regulatory system, AST device manufacturers initiate updating the breakpoint information used in the device labeling for a given drug after the manufacturer who produces that drug submits a labeling supplement to FDA, and FDA approves the supplement. The multiple steps to update the breakpoints adversely affect the public health by preventing AST device manufacturers from being able to update the breakpoint information in their devices promptly, and it utilizes resources that could otherwise be used for antibacterial and antifungal drug reviews, among other things.

Reviewing separate breakpoint labeling supplements for each individual drug product (even if they share the same active ingredients, and thus, generally have the same breakpoints) is no small task. There are approximately 200 reference-listed antibacterial drug products and more than 400 generic copies of those products. Moreover, the process begins with the submission of labeling supplements from the drug manufacturers, and although some drug manufacturers submit these promptly, the Agency needs to send others reminders. This approach to updating labeling is very resource-intensive from the FDA's perspective. The labeling of each reference listed drug (RLD) has to be addressed separately when, in fact, the breakpoints are often the same for all antibacterial drug products containing the same active ingredient, so there is a great deal of duplicate effort.

Many antibacterial drugs are very old, and they are now marketed only by generic firms. These companies often do not have staff with the technical expertise to evaluate and update the breakpoints. In addition to the 200 RLDs, there are approximately 400 additional generic systemic antibacterial drugs. It is expected that each generic firm will update their label when the RLD label for that generic antibacterial drug product is updated. The collective resources that are required of the pharmaceutical companies to update their drug product labeling and the associated FDA resources are/will be considerable, while most of this work will be to simply duplicate work previously performed to update the RLD label.

1.2 Does the FDA need new authority to ensure that antibiotic breakpoints are updated regularly?

FDA has begun to explore potential administrative options, at the same time as the Agency has been providing technical assistance to Congress on legislative options. Although we are

still working through the administrative options, there seem to be clear challenges associated with the ones we have identified.

- First, FDA Has Concerns that It Will Not be Able to Address this Issue Expeditiously – In order to address the issue comprehensively, FDA would likely have to take multiple administrative steps, including issuing several guidance documents and/or regulations to, among other things: (1) take the breakpoints out of the drug labeling, (2) recognize appropriate standard development organization standards, (3) explain the limited circumstances in which FDA may permit device labeling to contain information about bacteria that has not been identified in clinical trials, and (4) provide interested parties adequate notice about the new framework. The FDA Centers have been working together and are committed to addressing this issue, but each of these efforts could take 3-5 years due to the Good Guidance Practice processes and/or the notice-and-comment processes for issuing regulations.
- Second, FDA May Not Be Able To Execute Each Piece of the Administrative Strategy – If any one piece of the administrative strategy is delayed or stopped, the administrative approach would be less comprehensive, at best, and ineffective, at worst. FDA does not have complete control over whether and when documents are issued. Accordingly, if FDA began the process of executing an administrative strategy and developing a breakpoints website, neither FDA itself nor industry would have any certainty with regard to whether or when the new framework would be implemented.
- Third, Even If FDA Were Able to Issue an Entire Administrative Package, the Package Would Likely be Less Comprehensive than Legislation and Provide Less Certainty For Industry – Certain elements of the administrative strategy could require a fact-specific analysis, which would provide less certainty for industry than could legislation providing for an overarching framework.

Conclusion: FDA has determined that a legislative solution to the breakpoints issue is preferable to the potential administrative options that we have identified because it would: (1) address an increasing and significant public health issue much more expeditiously, (2) clarify FDA's authority to implement the program; (3) provide certainty to interested parties (and to FDA, before it invests resources in a new process) that a new framework will be put in place, and (4) address the problem more comprehensively.

1.3 Do the breakpoint provisions of H.R. 3742, the Antibiotic Development to Advance Patient Treatment Act of 2013 (ADAPT Act) address this matter sufficiently?

The breakpoint provisions of H.R. 3742 address a number of these issues; however, there are some modifications that could be made for the legislation to accomplish the bill's goal of enabling more timely updates of antibiotic breakpoints. We appreciate the Committee working with us to address these issues in H.R. 6. The modifications to H.R. 3742 include:

- Remove the breakpoint information from individual drug product labeling

altogether. This would allow AST device manufacturers to update their labeling, without waiting for the drug manufacturers to update their labeling first.

- Authorize FDA to: (a) recognize breakpoint standards, or portions thereof, established by Standard Development Organizations (SDOs), when the Agency agrees with the breakpoints, and (b) list other breakpoints on its website beyond what is in the drug labeling, when the Agency concludes such breakpoints are appropriate, along with appropriate language that can inform when such breakpoint information goes beyond the drug labeling. This would allow FDA to leverage its resources, while still ensuring that the Agency retains its authority to identify and update appropriate breakpoints.
 - Establish an FDA website where FDA-recognized breakpoint standards, as well as other appropriate breakpoints that are not covered by (or deviate from) FDA-recognized standards, would be posted. This website would: (a) allow FDA to update breakpoints for a drug, sold by multiple companies, at the same time, (b) make the latest breakpoint information instantly accessible to the health care community, (c) provide a centralized mechanism to help the health care communities track updates, and (d) make breakpoint information more transparent.
 - A device or drug manufacturer's use of breakpoints in FDA-recognized standards, or breakpoints otherwise listed on FDA's website, in submitting marketing applications is voluntary.
 - Individual drug and device manufacturers, including generic drug manufacturers, who disagree with FDA-recognized SDO breakpoint standards, or other breakpoints listed on the FDA website, may: (a) attend SDO meetings to weigh in on how SDOs should set breakpoints, (b) submit comments to FDA in response to the annual compilations of notices, in the *Federal Register*, which alert interested parties to breakpoint updates, and/or (c) submit marketing applications or supplements to FDA using different breakpoints.
2. **What are the challenges the FDA believe exist with regard to clinical studies for serious and life threatening antibiotics and how does this situation impact the setting of antibiotic breakpoints at the time of approval?**

Scientific Challenges Associated with Antibacterial Drug Development

There are several key scientific challenges associated with clinical trials of antibacterial drugs for serious and life-threatening infections:

Trial Enrollment: Patients with serious and life-threatening infections are very ill and may not be able to consent for themselves. Obtaining informed consent from such a patient or their family can be very difficult during this stressful time.

Prior Antibacterial Therapy: As patients with serious and life-threatening infections are very ill, antibacterial therapy needs to be started immediately as

any delay in therapy can have detrimental effects, including increasing mortality. These patients are often treated with non-study antibacterial drugs before they receive the new test drug, while the study enrollment procedures are underway. The antibiotics received before the trial may be the main reason the patient got better, not the test drug. This may make the trial results difficult to interpret as it may not be possible to determine the role of the new test drug in patient recovery.

Concomitant Antibacterial Therapy: At the time of enrollment, in most cases, the infecting microorganism is not identified. The infecting microorganism is definitively identified only when bacterial cultures are finalized about 48-72 hours later. During this early time period, non-study antibacterial drugs are administered empirically to provide coverage for likely potential causative microorganisms. Some of these non-study antibacterial drugs can have a spectrum of activity that overlaps with that of the test drug. This can confound assessment of the efficacy of the test drug.

Trial Conduct: As these types of studies are very difficult to conduct and enrollment at any one site is very slow, these studies are often conducted at multiple study sites (>100). In addition, to the difficulties with setting up several study sites, this can result in a significant increase in study costs.

Rapid Diagnostics: The lack of rapid diagnostic tests limits the ability to identify the infecting microorganism(s) within a few hours. It takes several days for the culture result to be available. Because of the delay in identifying the infecting microorganism(s), to ensure that a sufficient number of patients with the microorganism(s) of interest are included in the trial to allow for analysis, a larger number of patients have to be enrolled at the beginning of the trial.

Economic Challenges Associated with Antibacterial Drugs Development

We note that, in addition to the scientific challenges associated with studying a new antibacterial drug, the typical economic return on the marketing of antibacterial drugs is also an important factor that markedly limits what companies are willing to do (i.e., how much they are willing to invest) in order to properly study a new antibacterial drug.

Impact on Setting Breakpoints

The challenges with trials for serious and life-threatening infections do not impact the setting of susceptibility test interpretive criteria (breakpoints) per se. As these infections can be caused by a variety of microorganisms, often one may not identify any one particular microorganism in sufficient numbers to allow for setting of breakpoints based on this clinical trial data. Also, sufficient numbers of patients with microorganisms that are less susceptible are often not enrolled in clinical trials. This limits the amount of clinical data available regarding infections caused by these bacteria.

The Honorable Michael C. Burgess

- 1. You and the agency are leading champions of replenishing our antibiotic pipeline, but the economics are broken and HHS' own study on antibiotic incentives (*Incentives for the Development of New Drugs, Vaccines, and Rapid Diagnostics for Bacterial Diseases*) demonstrates that moving the needle in monetary terms for companies would take a reduction in clinical trials times by two to three years. Is that really possible? Can the ADAPT Act accomplish such? How else can FDA support bolstering the marketplace for antibiotics?**

The expected benefit of this legislation would be to encourage rapid development of antibacterial products to meet pressing unmet medical needs by conducting streamlined clinical trials enrolling fewer patients. Because approval in a smaller population with an unmet medical need could be based on limited data, drugs could be developed more quickly and less expensively than drugs undergoing typical antibacterial drug development. It is unlikely, however, that ADAPT's Limited Population Antibacterial Drug (LPAD) provisions would be able to reduce clinical trial times by two to three years. That does not mean that ADAPT would not help to bolster the marketplace.

In addition to providing a streamlined drug development process for addressing unmet medical needs, another positive outcome of the ADAPT legislation would be that it would likely contribute to an overall increase in the antibacterial armamentarium. More products representing different classes of drugs, many with different mechanisms of action, would make us better prepared to meet the unknown challenges of antibacterial resistance that lie ahead.

It is also critical that the ADAPT legislation that is eventually enacted require products approved via that pathway to have an LPAD pathway branding element, such as "LIMITED POPULATION" in close proximity to the brand name of the product. An LPAD branding element is critical to convey to all members of the health care community that the drug has been shown to be safe and effective for use only in a limited population. In order to make fully informed decisions, the health care community must understand that an LPAD drug was approved based on a unique benefit-risk profile in the indicated population and the safety and effectiveness of the product has not been demonstrated in broader populations. This is particularly important in the context of antibacterial drugs, which have historically been inappropriately overused.

Another way that FDA could support bolstering the marketplace for antibacterial drugs is to continue to work with companies to take advantage of existing expedited review pathways, such as fast track, qualified infectious disease product (QIDP) designation under GAIN, breakthrough therapy, priority review, and accelerated approval.

- 2. Even with accelerated approval, sponsors are still required to manufacture product batches on a large scale and perform long stability runs. To what extent has there**

been discussion at FDA to allow sponsors to build this over time, including after licensure, as this can be a rate limiting step to approval?

While there are general expectations related to the amount of stability data necessary to support approval of New Drug Applications, the Agency employs a risk-based approach in implementation of these expectations. In specific cases of clinical urgency and/or other types of public health impact, the Agency works collaboratively with Applicants to determine the most appropriate strategy for commercial scale manufacture and stability data submission. Alternate approaches include the submission of an abbreviated stability data package, adjustments to batch sizes used for primary stability data, and the use of supportive stability data in lieu of actual commercial scale primary data. These options are typically used for applications of high clinical urgency, including Breakthrough Therapies. The Agency has also found that a key part of successful collaboration with applicants, related to commercial scale manufacture and stability data submission, occurs when the applicant communicates challenges to the Agency as early in the process as possible. In the past, earlier communication with the applicant has enabled FDA to be a partner in solving some of these complex challenges and helped to bring these products to market in the shortest amount of possible time.

The Honorable Phil Gingrey

- 1. Congressman Green and I have been working on the ADAPT Act, which gives FDA greater flexibility to consider all forms of evidence, in addition to data from clinical trials, when setting breakpoints for new antibiotics at the time of approval. It is critical to ensure FDA has the tools required to incorporate the latest advances in science and modeling into its decision making process, especially when setting an antibiotic breakpoint at the time of approval. Does FDA agree with this statement?**

We already can use, and have been using, these types of information to make approval decisions. In addition to information from clinical trials, the Agency reviews data from studies conducted to understand the in vitro activity of the drug against large collections of bacteria of interest, studies to determine the efficacy of the drug in animal models of infection, and pharmacologic studies to predict the optimal dosing of the drug for greatest antibacterial effect. A thorough understanding of these types of data requires advanced analysis tools and familiarity with the best current thinking regarding the quality of the studies under review and the appropriate weighting of the various data types.

- 2. This Subcommittee has been a true leader in Congress to enact important reforms like the GAIN Act to stimulate development of important new antibiotics. We have also enacted mandates for FDA to update breakpoints for existing antibiotics in a timelier manner. For new antibiotics, the ADAPT Act would give FDA flexibility to consider all forms of evidence when setting their breakpoints – a parameter that guides the use of these drugs. Do you agree this would be an important reform to follow in the footsteps of what we have already done?**

Thank you for your leadership in this area. While we agree that it would be important to clarify FDA's ability to rely on such information in setting breakpoints, we already can use these types of information and have been using these types of information. The challenges faced in updating breakpoints are largely related to the processes involved in first updating breakpoints in a drug company's label for each of the many antibacterial drugs, then the device companies follow by updating their testing devices. The current process is inefficient, duplicative and not a timely mechanism for updating breakpoints in diagnostic testing devices. New approaches, some of which ADAPT contemplates, that leverage the work of standard development organizations (SDOs), take advantage of electronic means for updating (i.e., website), remove breakpoints from drug labeling, and affirm the Agency's recognition of interpretive criteria for bacteria not in the drug label could help to address the significant procedural challenges of updating breakpoints.

The Honorable Gus Bilirakis

1a. How many treatments were approved with novel biomarkers used for the first time within the last five years?

It is challenging to define biomarker novelty and to identify when such biomarkers were used for the first time. We are providing background information on biomarkers below and listings of a recent cohort of new drugs and accelerated approvals using biomarkers in Tables 1-3 in the enclosure to this response.

A biomarker is defined as:

“A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”¹

Biomarkers include laboratory tests (e.g., blood sugar or serum cholesterol), physical signs (e.g., blood pressure), and radiographic images, and are commonly used and relied upon throughout many phases of drug development from basic science, translational, and preclinical phases through to clinical testing. Biomarkers have many different uses. For example, they are used in pre-clinical animal toxicology testing to look for safety signals that indicate drug toxicity or target organ damage, in early phase clinical testing for pharmacokinetic and pharmacodynamic testing, such as to assess drug exposure and metabolism, guide dosing, assist with early safety evaluation, and to inform the design and conduct of later-phase trials, and in mid-to-later phase clinical testing, such as to assess early effects of intervention on biochemical pathways (such as LDL-cholesterol lowering). In pre-clinical and early clinical phase testing, these biomarkers may not directly factor into an approval decision for a marketing application, but the information gained from the use of biomarkers is usually critical to the development of drugs. In later-phase clinical testing

¹ Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69:89-95.

(e.g., Phase 3 efficacy or “pivotal” trials), in some circumstances a biomarker may be used as a surrogate endpoint.

Surrogate endpoints are a subset of biomarkers that are used as a substitute for a clinical endpoint in a clinical trial. A surrogate endpoint is defined as “a marker that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.”² Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may fall into one of three categories:³

- 1) The marker is *known* to predict clinical benefit; i.e., a validated surrogate endpoint that could be used as an endpoint in a clinical trial used to support a traditional approval. Some examples include HgA1C for diabetes medications and LDL-cholesterol (“bad” cholesterol) for statin medications used to treat hypercholesterolemia.
- 2) The marker is *reasonably likely to predict a drug’s intended clinical benefit*, and could be used as a basis for accelerated approval. An example includes tumor stabilization or shrinkage for some cancers, which is thought to be reasonably likely to predict an effect on overall patient survival.
- 3) A marker for which there is *insufficient evidence* to support reliance on the marker as either kind of surrogate endpoint, and that, therefore, cannot be used to support traditional or accelerated approval of a marketing application. An example includes HDL-cholesterol (“good” cholesterol) raising in clinical testing of a class of drugs (CETP inhibitors) intended to treat hypercholesterolemia and prevent cardiovascular disease. A trial for one such drug was halted when excessive mortality was seen in the treatment group despite the drug showing the intended pharmacologic effect of increasing HDL cholesterol levels in study subjects.⁴ A trial with another drug in this same class also raised HDL cholesterol but had a neutral outcome (neither harmful nor beneficial for the indication).⁵

Surrogate endpoints are most useful in settings where the disease course is long and an extended period of time is required to measure the intended clinical benefit of a drug. There may be many situations where the use of a clinical outcome assessment is more appropriate and where meaningful results can be more readily obtained.

For new drug development, many of the biomarkers, assays, tests, and measurements used during clinical development are product specific and need to be developed and tested during preclinical, early clinical, and later clinical phases of drug development. For example, markers of drug exposure (e.g., drug blood levels) or metabolism or, for biologic products, anti-drug antibodies, are commonly used in drug development and are likely to be product-

² Guidance for Industry. Expedited Programs for Serious Conditions –Drugs and Biologics at p. 17 (May 2014)
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>.

³ Ibid.

⁴ Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med.* 2007;357:2109-22.

⁵ Schwartz GC, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;367:2089-99.

specific (hence, novel). Thus, most new drug development programs will rely upon at least one (and often several) novel biomarker for product development and approval.

Novelty of a biomarker (or surrogate) can also include several different considerations:

- The biomarker may be entirely new and developed specifically for the drug development program.
- The biomarker (or surrogate) may have been available previously, but used for the first time for the disease or for the new drug (e.g., being adapted from a different disease or a different class of drugs).
- The biomarker (or surrogate) may have been available previously, but is now being used in a new way such as, as a surrogate endpoint when previously used as a pharmacodynamic measure.

There are thousands of drugs that have been approved over the course of FDA's extensive drug approval history. It would be extremely difficult to compile a comprehensive list of all drug and biological product ("drug") approvals for which a novel biomarker was used. Surrogate endpoints are commonly used to support both traditional and accelerated approvals for rare and common diseases, for new products (new molecular entity (NME)⁶ and original biologics) as well as for non-NME drugs and supplemental approvals (i.e., efficacy supplements).

We compiled the following list of primary endpoints used in clinical trials from a limited subset only of new product (NME and original biologic) approvals by FDA's Center for Drug Evaluation and Research (CDER) in a recent three-year period (January 1, 2010, through December 31, 2012 – please see Table 1, enclosed). These endpoints were classified as surrogates or clinical outcome assessments (COA) to illustrate the use of both these types of endpoints in product approvals. COAs are often defined as those endpoints that measure an effect upon how patients feel, function, or survive.⁷ Summary results are as follows:

- There were 85 new drugs approved in this time period: 29 for rare diseases (Orphan drugs) and 56 for common diseases.
- Of these 85 approvals, 40 relied upon a surrogate endpoint as the primary endpoint for the pivotal clinical trials, and 45 relied upon a COA:
 - For rare diseases, 20 of 29 (69%) approvals relied upon a surrogate endpoint.
 - For common diseases, 21 of 56 (38%) approvals relied upon a surrogate endpoint.

⁶ NMEs are defined as drugs for which the active pharmaceutical ingredient has not previously been approved by FDA.

⁷ Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. *Clinical Measurement in Drug Evaluation* New York, NY: J. Wiley; 1995. Pp. 3-22.

- Seven drugs received accelerated approval, all of which were based on a surrogate endpoint reasonably likely to predict clinical benefit, and all of which were for rare disease indications.

Given these factors, it is challenging to define biomarker novelty, and we do not feel that providing a listing on our part would be useful. Please refer to Tables 1-3, enclosed, for listings of a recent cohort of new drugs and accelerated approvals.

1b. How many treatments approved with novel biomarkers used for the first time were for indications other than cancer and HIV?

For the 85 new drugs listed in Table 1:

- Twenty-three drugs were for cancer or cancer-related indications and four were for HIV or HIV-related indications.
- For the 58 non-cancer, non-HIV-indicated drugs:
 - 22 relied upon a surrogate endpoint as the primary endpoint for approval
 - 36 relied upon a COA as the primary endpoint for approval.
- Seven of the 85 drugs received accelerated approval, five of which were for cancer indications and two of which were for non-cancer, non-HIV indications. There were no accelerated approvals for HIV drugs in this time period. The two non-cancer, non-HIV drugs included:
 - Ferriprox (deferiprone) for transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.
 - Sirturo (bedaquiline), indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug-resistant tuberculosis (MDR-TB).

The five cancer drugs included:

- Adcetris (brentuximab) for two indications: 1) systemic anaplastic large-cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen, and 2) Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.
- Xalkori (crizotinib) for locally advanced metastatic non-small-cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive.
- Kyprolis (carfilzomib) for patients with multiple myeloma who have received at least two prior therapies, including Velcade (bortezomib) and an

immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

- Synribo (omacetaxine mepesuccinate) for adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).
- Iclusig (ponatinib hydrochloride) for adult patients with chronic phase, accelerated phase, or blast phase CML that is resistant prior to TKI therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior TKI therapy.

1c. Have any accelerated approvals occurred with a novel marker and a never before treated disease?

Between October 1, 2007, and April 30, 2014, inclusive of NME and original biological products (NBE), supplemental approvals and non-NME NDAs, there were 40 Accelerated Approvals⁸ by CDER, including:

- Eighteen NME and original biologics Accelerated approvals (new drugs), and
- Twenty-two non-NME NDA or supplemental Accelerated approvals

The 18 novel product approvals are listed in the Appendix, Table 2. In summary, these include:

- Two Accelerated Approvals for HIV
- Twelve Accelerated Approvals for various Oncology indications
- Four non-HIV, non-Oncology Accelerated Approvals, which includes indications in the therapeutic areas of Hematology, Cardiovascular, and Infectious Diseases

The 22 non-NME NDA and supplemental Accelerated Approvals are listed in the enclosed, Table 3, including:

- One Accelerated Approval for HIV
- Sixteen Accelerated Approvals for various Oncology indications
- Five non-HIV, non-Oncology Accelerated Approvals, which includes indications in the therapeutic areas of Medical Countermeasures, Medical Genetics, and Obstetrics

Regarding novelty and disease indication, we note that the Accelerated Approval regulations require that drugs approved under this pathway generally provide meaningful advantage over available therapies. For example, many of the above disease indications are for refractory, resistant, or previously treated diseases where patients had previously failed one or several other available therapies, such as relapsed non-Hodgkin's lymphoma (NHL) and

⁸ CDER Accelerated Approval list updated through March 14, 2014 available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM404466.pdf>

tyrosine kinase-resistant chronic myelogenous leukemia (CML). While there are other drugs approved for these indications, refractory or relapsed NHL and CML are usually life-threatening diseases, and hence, these approvals were addressing unmet medical needs or providing patients with serious diseases and important additional treatment options.

1d. How many new biomarkers did the FDA accept for a first time use in the last five years?

Please see responses to Questions 1-3 above. Most drug development programs use biomarkers, and for new products, it would be expected that most (if not all) would use novel biomarkers. For descriptions of surrogate endpoints in a recent three-year period and accelerated approvals in a six-and-a-half year period, please see summaries above and Tables 1-3.

2. This committee led passage of the Pandemic and All-Hazards Preparedness Reauthorization Act last year. PAHPRA required FDA to establish a new process for frequent scientific feedback between the agency and developers of medical countermeasures under Project BioShield. These Regulatory Management Plans (RMPs) are critical to accelerating the review and approval of critical medical countermeasures against threats like anthrax, smallpox and Ebola. Will you describe FDA's efforts over the last year to implement RMPs with countermeasure developers?

Section 304 of PAHPRA amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to include a new mechanism—the Regulatory Management Plan (RMP)—whereby medical countermeasure (MCM) sponsors or applicants can interact with FDA regarding the development and regulatory requirements for eligible countermeasures. RMPs are agreed to by FDA and the product sponsor or applicant, and delineate developmental milestones that trigger meetings, written feedback, and decisions by FDA, or other activities (e.g., developing a plan to demonstrate safety and effectiveness in pediatric populations) conducted as part of the development and review process; associated performance targets and goals for such responses and activities; and how the plan will be modified if necessary. FDA has been coordinating with BARDA regarding the developmental stage of medical countermeasures that would most benefit from an RMP.

To date, FDA has not received any written requests for RMPs. This could be related to the proactive and flexible approach that FDA has employed to facilitate the product development of critical MCMS, as recently exemplified by those related to the prevention and treatment of Ebola Virus Disease (EVD), that provide heightened levels of interaction similar to those that might be expected under RMPs.

FDA provides MCM-focused regulatory advice and guidance through a variety of mechanisms, including direct engagement with sponsors and applicants, issuing guidance documents, and holding Advisory Committee meetings and public workshops. FDA medical product review centers have extensive interactions with MCM sponsors to discuss testing, data requirements, and scientific issues related to moving candidate MCMS into

clinical development and assessing progress as these specialized product candidates move through clinical development toward marketing application. FDA also provides technical assistance to minimize risk during MCM manufacturing, including pre-approval inspections or site visits to ensure that manufacturing establishments are capable of adequately manufacturing products, and that submitted application data are accurate.

FDA is fully engaged with our Federal partners to address MCM priorities and we continue to work with our Federal partners (e.g., HHS/ASPR/BARDA) to implement new authorities under PAPHRA. For a summary of these activities, please see our FY 2013 Annual Report at

<http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm390308.htm>.

3. PAHPRA strengthened FDA's Emergency Use Authority (EUA), and provided the agency more flexibility to get products to the public in an emergency. I am glad to see that FDA recently issued an EUA for a diagnostic test related to the on-going Ebola epidemic. Will you provide more details on the agency's use of these new authorities for Ebola? Are there more tests or therapies that may become available soon to health care workers on the front lines of Ebola?

FDA is using all of its emergency use authorities to the fullest extent possible to fulfill its mission to protect and promote the public health. FDA is actively working with Federal colleagues, industry, and international organizations to facilitate development, including evaluation of safety and efficacy, of treatments, vaccines, and diagnostic devices with potential to help mitigate the Ebola epidemic. We are reaching out proactively to multiple medical product developers to clarify regulatory requirements, provide input on pre-clinical and clinical trial designs, and expedite review of data as they are received from product developers. These efforts should help advance the development and availability of investigational products as quickly as possible.

FDA has one of the most flexible regulatory frameworks in the world, which includes mechanisms to enable access to investigational medical products when appropriate, after the risks and benefits to the patient have been weighed. To date, FDA has issued EUAs to allow the use of nine diagnostic tests developed by the Department of Defense, the Centers for Disease Control and Prevention and commercial sponsors for use in certain laboratories during this Ebola epidemic. We were able to issue these EUAs, in part because of new authorities gained under PAHPRA, which provide greater flexibility in the issuance of EUAs. We are encouraging other product developers of investigational diagnostics to test for Ebola to submit data to FDA for EUA consideration.

While FDA is making every effort to encourage development, speed review, and use flexible approaches to authorize the use of potential medical products to address Ebola, investigational vaccines and treatments for Ebola are in the earliest stages of development for this purpose. Data on safety and/or effectiveness in humans are limited or lacking, and accurate assessment (especially of effectiveness) may be impossible if adequately designed clinical trials are not performed. Also, for most of the investigational drugs, only small amounts have been manufactured for early testing. This supply issue constrains the options

for properly assessing the safety and efficacy of these investigational products in clinical trials to respond to the epidemic, and also limits the possibilities for making investigational products available for therapeutic use outside of a clinical trial. Nonetheless, while investigational products are being developed, with the ultimate goal of product approval and manufacturing for wide-scale use, FDA is doing all it can to facilitate appropriate levels of access to these products when the clinical circumstances warrant. Access to investigational drugs used to treat Ebola outside of clinical trials has been effectively facilitated under FDA's expanded access mechanisms (e.g., emergency investigational new drug (eIND) requests). There has been no need to issue an EUA to facilitate broader access to these investigational drugs. That said, FDA is fully prepared to issue an EUA to enable broader access to investigational drugs for Ebola if the need arises and the scientific data warrants its issuance.

4. One of the challenges we have heard from countermeasure developers who are partnering with the federal government is that communication between FDA and the Biomedical Advanced Research and Development Authority (BARDA) has been severely lacking. This makes it difficult for developers to be confident that these high-risk projects, including drugs to combat antimicrobial resistance, can be ultimately be successful? What is FDA doing to improve communication with BARDA as it relates to countermeasure development?

FDA's overarching objective with respect to MCMs is to facilitate the development of and access to safe and effective countermeasures to counter high-priority chemical, biological, radiological, and nuclear threats and emerging infectious disease threats. FDA works extensively with the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) partners led by the HHS Office of the Assistant Secretary for Preparedness and Response, and including BARDA, to pursue this objective and support MCM-related public health preparedness and response efforts.

FDA also provides subject matter expertise and technical assistance to numerous standing PHEMCE-specific committees and working groups that develop MCM requirements, plans, priorities, and policies and conduct program oversight and integration. These standing committees and working groups meet on a weekly, monthly, bimonthly, quarterly, semi-annually, or as-needed basis depending on the requirements of the issues at hand. These committees and working groups address a range of topics across the full spectrum of activities associated with MCMs from threat assessment to requirements setting to product development to procurement, stockpiling, and utilization. With regard to the example presented in the question, FDA is an active member of the standing PHEMCE working group that meets regularly to address the threat of antimicrobial resistance in addition to other government-wide working groups. In addition, FDA participates in BARDA's "In-Process Reviews" to evaluate the progress of medical countermeasures which BARDA has under contract with the sponsors of those medical countermeasures.

In addition, to ensure that the MCMi Regulatory Science Program is appropriately targeted and coordinated with U.S. government MCM priorities, FDA established a Steering Committee (which includes BARDA) to evaluate research proposals for scientific/technical merit and feasibility as well as for alignment with PHEMCE priorities. The goal of the

MCMi Regulatory Science Program is to develop the tools, standards, and approaches to assess MCM safety, efficacy, quality, and performance and to help translate cutting-edge science and technology into innovative, safe, and effective MCMs—including for at-risk populations.

To facilitate this level of engagement, FDA and the PHEMCE, including BARDA, have a Memorandum of Understanding (MOU) in place to establish a framework to promote efficiency and collaboration between FDA and PHEMCE partners. Moreover, FDA and the ASPR/ BARDA have a separate MOU in place to explore ways to further enhance information sharing efforts through more efficient and robust interagency activities; promote efficient utilization of resources and expertise for development of safe and effective medical products regulated by FDA for use as MCMs; support development of collaborative processes that meet the common needs for supporting medical product development and innovation; and assist the industry so they may advance product development with core technical expertise and regulatory guidance, build manufacturing infrastructure, and surge capacity for medical products regulated by FDA for use as MCMs.

If you have more specific information about communication challenges between FDA and BARDA from countermeasure developers, we welcome follow-up to better understand the challenges identified.