



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
House of Representatives
Washington, D.C. 20510-3816

NOV 24 2014

Dear Mr. Chairman:

Thank you for the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the July 11, 2014, hearing before the Subcommittee on Health entitled "21st Century Cures: Incorporating the Patient Perspective." This letter provides responses 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 stylized flourish at the end.

Thomas A. Kraus
Associate Commissioner
for Legislation

Enclosures

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

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

The Honorable Michael C. Burgess

- 1. I asked about this in early April, but I do not believe I have received a response. Do you have any update on the status of the FDA's guidance on biosimilars naming? When will this guidance become final?**

FDA is currently considering the appropriate naming convention for products licensed under the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, enacted as part of the Patient Protection and Affordable Care Act (P.L. No. 111-148). As part of this endeavor, the Agency is carefully reviewing the comments on naming submitted by stakeholders to FDA's biosimilar draft guidance and public hearing dockets, or that otherwise have been submitted to FDA. The Agency will adhere to its good guidance practices in issuing any draft guidance on this topic.

- 2. Has anyone outside of FDA provided the agency with substantive suggestions or recommendations with respect to this guidance? If so, please provide the name of the person or persons who provided those suggestions or recommendations, and any action FDA took in response to those suggestions or recommendations.**

See response to Question 1.

The Honorable Gus Bilirakis

- 1. How many treatments were approved with novel biomarkers used for the first time?**

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

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

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 (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.

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.

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-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, was used 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 in 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.
 - 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.

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.

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.

2. 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:
 - Deferiprone (Ferriprox) for transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.
 - Bedaquiline (Sirturo) indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).

The five cancer drugs included:

- Brentuximab (Adcetris) for two indications: 1) systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen, and 2) Hodgkin 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.
- Crizotinib (Xalkori) for locally advanced metastatic non-small cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive.
- Carfilzomib (Kyprolis) for patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.
- Omacetaxine (Synribo) 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).
- Ponatinib (Iclusig) 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.

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

For the most recent ~6.5-year Accelerated Approval⁸ experience at CDER inclusive of NME and original biological products (NBE), supplemental approvals and non-NME NDAs, approved by CDER between October 1, 2007, and April 30, 2014. There were 40 Accelerated Approvals during this time, 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 Disease

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-Hodgkins lymphoma (NHL) and 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, and hence, these approvals were addressing unmet medical needs or providing patients with serious diseases important additional treatment options.

4. 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.

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

For descriptions of surrogate endpoints in a recent 3-year period and accelerated approvals in 6.5 years period, please see summaries above and tables 1-3 in the Attachment.

The Honorable Kathy Castor

- 1. I want to bring up an issue I sometimes hear from my patients on the Central Coast. As you know, a number of states have passed legislation known as right-to-try laws. In general, they allow drug companies to provide unapproved drugs to patients whose doctors request them, so long as the drugs have passed some level of safety testing. The laws eliminate the need for patients to get a compassionate use exemption from FDA. These laws appear to be based on a misperception that FDA either routinely denies such requests, or that such requests entail lengthy and complex paperwork. I know this is a complicated and often heart-rending issue. However, it seems that when patients have difficulty getting access to experimental drugs, it is because the drug company does not wish to provide it, not because FDA has prevented access.**

Could you describe for us the process FDA has for providing patients with compassionate use access to experimental drugs, including how long it takes and how cumbersome the process is? Why might companies not want to provide their experimental drugs to patients in desperate need? I would also like to know what types of concerns these right-to-try laws raise for FDA. Thank you.

Expanded access, sometimes referred to as “compassionate use,” is the use of an investigational drug outside of a clinical trial, for the sole purpose of treating a patient or patients with serious or life-threatening disease(s) or condition(s) who have no acceptable medical options.⁹ FDA has a long history of facilitating access to investigational drugs for treatment use. As a result of this, tens of thousands of patients with serious or life-threatening diseases or conditions such as HIV/AIDS and cancer have had access to promising therapies when there is no comparable or satisfactory therapeutic alternative. There are specific expanded access provisions in both FDA’s statute and its regulations that address this process.

By way of background, FDA cannot require a pharmaceutical company to provide an unapproved drug to patients. Availability of an investigational product through expanded access depends on the agreement of the company to make the drug available for the expanded access use, either through the company’s own expanded access program or to a treating physician for administration to his or her patient.¹⁰

FDA’s regulations balance access to promising new therapies against the need to protect patient safety. Additionally these rules seek to ensure that expanded access does not discourage participation in clinical trials or otherwise interfere with the drug development process. Clinical

⁹<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies.ucm177138.htm>

¹⁰ See FDA web site, “Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use,”

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication.ucm107434.htm>

trials are the most important part of the drug development process because the results from the trials are used to evaluate whether new drugs are safe and effective for the studied indication(s) and, if the drugs are approved, how the drugs should be labeled.

A request for expanded access can be submitted either (1) as a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use, or (2) as an access protocol submitted as a protocol amendment to an existing IND. The number of requests for expanded access INDs and protocols can be found on the FDA Internet website at

For CDER:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373560.htm>.

For FDA's Center for Biologics Evaluation and Research (CBER)

<http://www.fda.gov/BiologicsBloodVaccines/ucm413041.htm>.

As a general note, INDs are not "approved" but rather are either allowed to proceed or not allowed to proceed, and expanded access is a type of IND. FDA's website above includes information on how many expanded access INDs were allowed to proceed. We note that in FY 2013, for CDER, the number of expanded access INDs and protocols allowed to proceed was 974 out of 977 received (99.7%). For CBER, from October 2009 through September 30, 2013, the number of expanded access INDs and protocols allowed to proceed was 226 out of 236 (95.7%).

The time frames are the same for expanded access INDs as for other INDs: unless FDA places the IND on clinical hold, an expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA. For expanded access protocols, expanded access use for individual patients and intermediate-size patient populations may begin after both Institutional Review Board (IRB) approval has been obtained in accordance with FDA regulations (21 CFR part 56) and the protocol has been submitted to FDA. Expanded access use under a treatment protocol may begin 30 days after FDA receives the submission or on earlier notification by FDA, and after IRB approval has been obtained.

We note that there are FDA physicians available on a 24-hour basis so that, when appropriate, an expanded access IND can be allowed to proceed immediately, following a phone call with FDA staff. For expanded access INDs for individual patients, frequently referred to as Single Patient INDs, INDs are often reviewed in less than one week, and sometimes in just a few hours, as the submission is for one patient and the information submitted tends to be smaller in volume. Expanded access INDs for intermediate-size or large patient-populations tend to be larger in size and more complex, so the full 30 days often are needed to review these types of submissions. If FDA completes its review in less than 30 days and determines the IND may proceed, we will notify the sponsor.

The Administration has not taken a position on any state's 'Right to Try' bill.