American Association for Cancer Research
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July 22, 2014
Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-0363 "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions"

To whom it may concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the April 2014 draft guidance on "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions."

The AACR applauds the FDA for developing a draft guidance outlining a new, voluntary program to help patients have more timely access to life-saving medical devices including *in-vitro* diagnostic devices. There are, however, a few areas in which we believe additional guidance would be beneficial. Specifically, the AACR requests FDA to provide greater clarity and detail on the definition of "breakthrough technologies", acceptable post-approval studies, alternative mechanisms of evidence gathering, use of surrogate end points, use of the EAP pathway in conjunction with other expedited pathways for medical products and the logistics of implementing this ambitious new program in a potentially resource constrained environment among other issues. We have elaborated on these concerns below.

With these additions, we believe the guidance document will clarify the pathway to expedite development and approval of novel medical devices intended to fulfill an unmet medical need for life threatening diseases like cancer and create new hope for cancer patients worldwide.

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Pathway nomenclature

The pathway as currently named is the "Expedited Access PMA" or EAP pathway. We would like to draw the Agency's attention to an existing pathway that shares this exact acronym namely the "**E**xpanded **A**ccess **P**rogram" (EAP) which allows patient access to experimental drugs outside a clinical trial through a single patient Investigational New Drug (IND) mechanism. To avoid confusion, we suggest the Agency rename the pathway the "**Accelerated Access Pathway**" or AAP. As the draft states, the proposed new pathway is based in part on existing expedited development programs at the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), namely the Accelerated Approval pathway for drugs and biologics. Thus, we urge the Agency to consider AAP as a viable alternate name for the pathway since it would be parallel and analogous to the mechanism and nomenclature of the existing pathway for drugs and biologics and would help avoid confusion.

Explicitly define "breakthrough technology"

The draft guidance states that a product may qualify for the Expedited Access PMA or EAP designation if "*The device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology*".

It would be helpful if the Agency could clarify what it means by a "breakthrough technology". For example, could an assay based on existing and commonly used technology (such as immunohistochemistry) be considered breakthrough if it provided a clinically meaningful advantage when used with a highly effective therapeutic?
Multiple *in vitro* diagnostic devices or IVDs could be developed using a breakthrough technology such as next generation sequencing or NGS technology. In such a case, the Agency should clarify whether all IVDs that utilize the same underlying cutting-edge technology, such as NGS, could qualify for the EAP designation or whether the designation could only be given to the first application of the technology.
Further technology is constantly evolving and what is considered innovative today will eventually become a routine and common procedure. Therefore, it would help if the Agency could provide some broad, high-level guidelines on its thinking about how it would define and designate a "breakthrough technology".

Provide clarity on the implementation of the EAP pathway

The draft states that "*FDA may approve more than one EAP device for the same condition because of the possibility that the data from the post-approval study may not*

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confirm certain safety or effectiveness aspects of the device under the conditions of use. FDA may therefore consider devices as offering a "significant, clinically meaningful" advantage over existing approved alternatives, notwithstanding the availability of an EAP Device approved on the condition of a post-approval study."

It would be helpful if the Agency could elaborate on how it would interpret and implement this section of the guidance. For example, a plausible scenario is as follows: two products receive EAP designation for the same condition and one product gains approval before the other.
This above situation raises several questions including but not limited to the following:

- Would the second EAP designated product subsequently have to demonstrate evidence of "*significant, clinically meaningful advantage"* over the first EAP designated product?
- Would the details of the data development plan change for the second EAP designated product, even if previously agreed upon by both the sponsor and the Agency?
- If so, would the Agency continue to work with the sponsor to aid in revising the data development plan? and
- Would the burden of proof for demonstrating *significant, clinically meaningful advantage* differ from proving safety and effectiveness?

With respect to the concern that the "*…data from the post-approval study may not confirm certain safety or effectiveness aspects of the device…",* it would be helpful if the Agency could clarify whether this would result in a "revision" to a specific aspect of the device in question or whether it would entail something more. For example, perhaps a cutoff value for a biomarker based *in vitro* diagnostic assay would change based on data obtained in the post-marketing setting which may necessitate recalibration of the device. It would also help if the Agency could elaborate on how the data obtained from post-approval studies would be used to refine or revise the product in the post-marketing setting including the logistics of informing the sponsor of changes to the product, ensuring implementation of these changes while the product is on market, timeline for implementation of changes etc.

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Clarify use of EAP pathway in conjunction with existing expedited pathways for approval of drugs and biologics

The EAP draft guidance states that "…*certain companion diagnostics, when appropriate, and with consultation from CDER or CBER, may be considered for the Expedited Access PMA. For example, if a drug is reviewed via the accelerated drug approval pathway based on a surrogate endpoint, the companion diagnostic may be considered for the Expedited Access PMA*."

We welcome the Agency's willingness to consider a companion diagnostic for the EAP designation if its corresponding therapeutic partner is granted expedited review via the accelerated approval pathway. However, the Agency should clarify the status of the companion diagnostic in a situation wherein the therapeutic product fails its confirmatory study since an investigational drug or biologic is granted accelerated approval on the condition that the sponsor will conduct post-market confirmatory studies and with the understanding that the Agency has authority to withdraw approval for the drug or biologic if the confirmatory studies fail to meet the appropriate clinical end point. We also request that the Agency provide more details on the processes and procedures whereby sponsors can coordinate filing requests for accelerated approval of the therapeutic product and the EAP designation for its companion diagnostic.

Given that the recent "Breakthrough Therapy designation" has provided a great opportunity to expedite approval of therapies especially in oncology, the Agency should clearly state whether companion diagnostics to Breakthrough Therapy designated products may also be considered for the Expedited Access PMA. Further, given that most oncology therapies under current development are targeted therapies with a companion diagnostic, the Agency may want to consider automatically granting EAP designation to the companion diagnostic of breakthrough designated and accelerated approval pathway products.

Provide greater details on acceptable post-marketing studies

The EAP program will rely heavily on post-marketing studies to provide additional evidence of the safety and efficacy of the device. However, the guidance fails to give details of situations or examples of post-market studies that may be appropriate. We note that the Agency has released draft guidance on *Balancing Premarket and Postmarket*

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Data Collection for Devices Subject to Premarket Approval[1] in which there is one example of a situation where postmarket data collection may be appropriate for an IVD.

"Example: *HPV testing devices have two distinct intended use populations with inherently different risk levels for cervical pre-cancer and cancer. Approval for both populations was based on full analytical data and agreement of clinical samples against a valid comparator, and clinical evidence of safety and effectiveness for the high risk population. A post-approval study assessed the longitudinal risk of cervical cancer in the population with lower risk*."

However, given the diversity of IVD products it would be helpful for the Agency to give more examples of situations where post-market data studies would be appropriate for an IVD seeking EAP approval. It would also be helpful if the Agency could provide details on what kinds of information can be relegated to post-market studies by sponsors who are planning to file for an EAP designation. In other words, it would be helpful if the Agency could clarify whether they are primarily interested in collection of serious adverse effects or long-term safety or product effectiveness etc.

The draft states that "…*FDA may require a bridging study to evaluate the potential impact of various changes (e.g., specimen processing or storage, device or software modifications) on analytical and clinical performance*."

The Agency should clarify whether these bridging studies should be conducted in the pre or post marketing setting. We also refer the Agency to our concerns about interpretation of data from post-approval studies not confirming certain safety or effectiveness aspects of the device detailed earlier in this comment letter. We request the Agency to clarify whether bridging studies can be carried out and/ or may suffice in cases where post-approval studies raise concerns about the quality of a product.

Establishing safety and efficacy of IVDs requires establishing not just analytic and clinical validity, but most importantly clinical utility. Collecting clinical utility data often involves conducting clinical studies which can be expensive and time consuming. The

[1] Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval: FDA Draft Guidance issued on April 23, 2014. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393994.pdf

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draft guidance, however, does not mention collection of clinical utility data. Therefore, it would be helpful if the Agency could clarify whether clinical utility data may be collected in the post-market setting if the IVD qualifies for an EAP designation and elaborate on how data collection in the post-market setting should be implemented.

Provide greater detail on acceptable evidence

The draft states that "*In the absence of a new prospective clinical study, FDA may in some cases accept alternative experimental designs unique to diagnostics to generate evidence demonstrating the analytical and clinical validity of an IVD for premarket approval*." One of the examples given is: "*In cases where the clinical validity of a biomarker test may be fully established in the literature, only analytical data that demonstrate a genetic test can accurately detect the variant may be necessary*."

Given that studies in literature span the gamut from early observational studies to studies in validated animal models to reports of clinical trials, it would be helpful if the Agency could clarify, detail and elaborate on what level of evidence and what methodology of study constitutes "*fully established clinical validity of a biomarker test*" in the literature.

With respect to Companion Diagnostics, the draft states that "*In some situations (e.g. a test that combines multiple analytes into a score), a reference method may not exist for direct analytical comparison. In these instances, alternative approaches to address analytical performance may be appropriate*."

We commend the Agency for including this forward-looking concept in the draft. However, it would be helpful if the Agency could provide concrete examples of methodologies and/or kinds of studies that would be acceptable "alternate approaches" to address analytical performance of IVDs and companion diagnostics. We acknowledge the difficulty of providing such comprehensive information *a priori*, therefore, we urge the Agency to provide as much detail and clarity as possible on this issue which is of great importance and concern to the field.

Clarity on the use of surrogate end points

The draft states: "*FDA may, as a basis for PMA approval, rely on assessments of a device's effect on an intermediate or surrogate endpoint that is reasonably likely to predict clinical benefit...*"

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As an example, the draft provides the following: "*Early pathophysiologic analysis of biopsied breast lesions is not a direct measure of clinical benefit but has been shown to correlate with and predict morbidity and mortality associated with breast cancer. Pathophysiological analysis of biopsied breast lesions could serve as a surrogate endpoint for device trials, provided there is sufficient evidence of a known or reasonably likely predictive relationship with clinical benefit such as survival.*"

It would be helpful if more examples of acceptable surrogate and intermediate endpoints could be provided. It would also be helpful if the Agency could provide details of currently accepted surrogate and/or intermediate endpoints for approval of IVDs and companion diagnostics especially in oncology. The Agency should also clarify the conditions as well as the process by which a sponsor could use a novel surrogate or intermediate end point to provide evidence of a device's efficacy and/or safety.

An important consideration for researchers and developers of oncology products is the use of surrogate end points to qualify a therapeutic and its companion diagnostics. We request the Agency to clarify whether the "clinical benefit" of a companion diagnostic demonstrated using a surrogate end point or otherwise, will be judged or considered independently of its corresponding therapeutic product.

Logistics of implementing the EAP program

The draft states that "*As part of this EAP program, FDA intends to provide, **as resources permit**, more interactive communications during device development and more interactive review of Investigational Device Exemption (IDE) applications and PMA applications. In addition, FDA intends to work interactively with the sponsor to create a data development plan specific to the device ("Data Development Plan"). This Data Development Plan should outline all data the sponsor intends to collect in support of device approval, including what data will be collected premarket and postmarket.*"

We enthusiastically welcome the Agency's willingness to consider a pathway to expedite development of life-saving medical devices. However, it is concerning that the Agency uses the phrase "**as resources permit**" to qualify its ability to provide more interactive communications. It would be helpful if the Agency could elaborate on its thinking around how it plans to implement this exciting new, albeit potentially resource intensive program. We specifically request that the Agency clarify the meaning and intent behind the phrase "**as resources permit**" and elaborate on how it plans to determine whether it has adequate resources to man the program and further whether and how it plans to

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communicate its resource availability to researchers and developers who wish to avail themselves of the EAP program. Of concern to us is, whether the Agency can deny a potential EAP designation to a product that fully merits the designation, solely on the basis of a lack of Agency resources. This also leads to a concern that EAP designations will be limited by the Agency's resource constraints or EAP designations will only be considered when and if the Agency decides it can spare adequate resources, which we acknowledge may fluctuate from time to time. The question of resource availability also poses concerns about the Agency's ability to work with sponsors on the "data determination plan" which is a central and crucial component of obtaining the EAP designation. Since the main advantage to sponsors granted the EAP designation is the ability to work with the Agency to create the Data Development Plan and have interactive communications during product development, it is unclear how a sponsor may benefit from the EAP designation if the Agency grants the designation, but subsequently decides it is resource constrained and therefore cannot offer the above benefits to the sponsor.

The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework. The AACR is pleased to extend its resources and broad expertise to the FDA as the Agency further considers revisions to the April 2014 draft guidance on "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions". If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Director, Regulatory Science and Policy at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,

Frank McCormick, PhD, FRS
Chair, Regulatory Science & Policy Subcommittee

Margaret Foti, PhD, MD (h.c.)
Chief Executive Officer

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