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The Forum for Collaborative HIV Research, an independent public/private partnership that includes government agencies, pharmaceutical and diagnostic industries, HIV researchers and clinicians, payers, foundations, and the HIV patient advocacy community organized a roundtable discussion on February 16, 2007 to discuss how current and future HIV antiretroviral expanded access programs (EAPs) might be improved so that they best meet the needs of patients, clinicians, industry sponsors, and regulatory agencies. This roundtable meeting was the first opportunity for all of the relevant parties to talk about improving expanded access programs for antiretroviral agents. As such, it was a valuable opportunity not only to listen to the concerns and perspectives of the various constituencies, but also to realize how much their interests align in support of providing access to therapies for patients with few treatment options.

We submit the following comments and recommendations to the FDA Docket No. 2006N-0062 and RIN 0910-AF14.

Introductory comments:

Expanded access programs were developed in order to make promising treatments available to patients who need them as early in the drug evaluation process as possible. In particular, the goal is to make such drugs available to patients who have exhausted all currently approved therapies. Early in the HIV epidemic, HIV activist organizations challenged the existing drug approval system as too cautious, particularly in the face of a deadly epidemic that was claiming thousands of lives for lack of effective therapies. Their efforts shifted the balance from the strictly protective model with an emphasis on preventing harm to patients toward increasing access to potentially effective therapies for patients who are in need.

The HIV field likely has the most experience with expanded access programs compared to other diseases. Twenty-one drugs have previously been made available through expanded access programs in the United States and an additional three drugs are currently available through expanded access programs for people living with HIV.

At present, the approach to EAPs is to have each company's program (independent of other companies) precede the release of new antiretrovirals prior to FDA approval. Major concerns to this approach within the HIV scientific, medical and activist communities include the increased risk of drug resistance when adding a single new agent to a failing regimen (or "virtual monotherapy"), potentially leading to a transient response but reduced long-term durability; and the risks associated with using untested combinations of drugs before the potential for drug interactions has been systematically studied.

Key issues in HIV-therapy related EAPs:

- The size of the patient population that currently needs access to investigational antiretroviral drugs is difficult to estimate. We recognize that such patients do still exist and that the size of the

population is probably decreasing, but convincing data to indicate the number of patients in need of early access is lacking. In addition to the criteria of failing a third regimen, a key factor in the equation is the urgency of the patient's need for new therapy.

- Tension exists between the clinical and research aspects of EAPs. While the primary rationale for EAPs is to provide early access to drugs for patients in need, there are secondary competing interests in terms of the requirements to collect useful safety data on emerging compounds that might identify unknown safety issues and ultimately help guide treatment strategies. However, current data collection practices rarely yield useful information.
- EAPs are associated with a heavy administrative burden that limits the ability of some sites to participate and these programs are unfunded or underfunded. This burden appears to be particularly acute in the academic research setting, where intensive IRB approval and oversight combined with the data collection requirements of the protocols has forced some centers to forego participation in EAPs until they can find a way to pay for them. As sites refuse to participate, this limits patient access to the EAP.
- EAPs need to be conceived of within the context of clinical strategies overall. As the HIV epidemic and antiretroviral treatment strategies have evolved, it is no longer advisable to give patients new drugs without ensuring other active agents in the regimen. Otherwise patients would effectively be receiving virtual monotherapy and risk the development of drug resistance and subsequent regimen failure.
- Geographic limitations continue to impede access for patients in small cities and in rural areas. Ideally, the system should be able to provide access to experimental drugs for all patients who need them and qualify for EAPs regardless of where they live.
- Information about the EAPs can be quite difficult to find. Some companies do not list sites participating in their EAP on their own websites or on database websites like clinicaltrials.gov, making it very difficult for patients and their physicians to know where they might access experimental agents outside of clinical trials. Similarly, companies may not adequately advertise the existence of their EAPs. Industry is particularly concerned about the perceived appearance of pre-approval marketing.

Specific Recommendations:

- Explore the potential for standardization of EAP data collection requirements and safety reporting. This could reduce the redundancy in the current system and simplify participation in multiple simultaneous EAPs.
- Consider further collaboration between regulatory agencies and the pharmaceutical companies in the design of EAPs to include the simultaneous use of multiple investigational agents and to identify creative study designs that will limit the use of virtual monotherapy and address the evolving therapeutic needs of patients.
- Explore standardizing EAP protocols so that some of the administrative work (example being submission to IRBs) can be lessened.
- Explore the potential collaboration between the FDA and other regulatory bodies to standardize and minimize the burden, as much as possible, for the very complex and variable regulatory requirements for EAPs.
- Explore how the pharmaceutical companies can standardize their EAPs in terms of development of case report forms and adverse events reporting.
- Provide guidance to contract research organizations (CROs) on data collection requirements such that the administrative burden for an EAP is reduced compared to a standard clinical trial.
- Apply and take advantage of technological modernization in adverse event reporting. For example, a centralized electronic database could provide access to basic tabulation and analysis

of the voluminous serious adverse event reports that in their present form are virtually useless to the individual site investigators and site IRBs.

- Consider a two tiered expanded access approach: one would be an actual research protocol designed to address specific questions leading to approval, and which would be appropriately reimbursed like any other clinical trial. Such a protocol could address the types of issues normally studied in Phase 4 studies. These could be designed to target underrepresented patient populations. The second parallel approach could be a simplified protocol, similar to the current EAP protocols. However, both tiers likely would need reimbursement to participating institutions due to non-recovered costs of participation in the EAP.

A full report from this roundtable discussion will be available on the Forum for Collaborative HIV Research's website at <http://hivforum.org/projects/Expanded%20Access.htm>

Forum for Collaborative HIV Research
RETHINKING THE APPROACH TO EXPANDED ACCESS PROGRAMS

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