January 30, 2013

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Comments of the Patient and Consumer Coalition
"Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need"
Public Hearing
[Docket No. FDA-2012-N-1248]

As members of the Patient, Consumer, and Public Health Coalition, we recognize the need for new drugs to reach patients with serious or life-threatening diseases. However, based on our knowledge of existing accelerated approval strategies and the widespread off label use of prescription drugs, we have grave concerns about the creation of a new, vaguely defined pathway intended to approve drugs for limited populations.

There are currently six mechanisms designed to facilitate the expedited development and review of drugs to "address unmet medical need," some of which are based on extremely small studies. How effective are the existing pathways, and in what way is this new pathway needed or likely to be superior? Moreover, in the PCAST recommendations, from which this proposal was derived, the council understood that such a pathway would be ineffective without overhauling FDA's approval and regulatory processes to protect patients.[1] No such overhaul is underway.

Until the FDA has persuasively shown that a new pathway is needed and will not foster the development of drugs with unproven benefits that leave vulnerable populations at risk for death and other serious adverse effects, we cannot support this proposal.

We highlight our major concerns below.

A new pathway for drug approval for small, limited populations is not needed because it will not promote faster access to safe and effective treatments.

Based on the way the FDA applies the six existing pathways, we estimate that 40% of drugs approved every year already meet the qualifications for expedited review or approval. Additionally, the FDA has the flexibility to adjust indications for broad or narrow populations and already does so in some cases to approve new drugs based on exceptionally small clinical trials or high risks for the majority of patients.

Since the new pathway would rely on studies with fewer patients and reduced follow-up times, the FDA needs to make a stronger case to explain why this new pathway is needed. The FDA proposal has not indicated how such a pathway could accurately identify benefits, and for whom.

Limited population studies will not provide the patient-centered data needed to ensure that patients benefit from the new drugs. Without conclusive benefit, no increased risk should be acceptable.

To improve access to new and better treatments, the FDA needs to refine the standards for clinical testing of new drugs. The FDA has been making some approval decisions based on clinical trials that are poorly designed and use inappropriate surrogate endpoints rather than only accepting ones relevant to patients, which reflect mortality and quality of life. Additionally, the drugs will not be adequately tested in the target populations. It is difficult to identify specific target populations of patients with "serious unmet needs" because diagnostic tools are out of date and co-morbidities cloud identification of treatable patients. Instead, the approval of a drug through this new pathway will be based on ad hoc analysis from larger studies without scientific proof of safety and efficacy. With such limited clinical trials, there will be insufficient evidence to prove these drugs actually meet patients' serious needs.

The proposed new approval pathway does not address either how small clinical studies will adequately show a benefit to patients nor how an appropriate population will be identified. Instead, as physicians attempt to determine who will benefit based on limited clinical trial data, millions of patients will be put at risk as drugs with unproven benefits and unknown risks remain on the market for years before even the most serious adverse reactions are identified through larger, post-market studies. As currently outlined, the proposal leaves room for approval of drugs without conclusive benefit, exacerbating the problems of antibiotic resistance and disease progression.

Without effective policies to prevent misbranding and illegal promotion, millions of other consumers will also be put at risk.

Even if a drug is approved for a small, targeted population, the FDA has neither the resources nor the authority to restrict promotion and misbranding of drugs. There is clear evidence that companies will advertise these

products widely, thus attracting consumers well beyond the targeted, defined population who would be most likely to benefit. Without appropriate regulation and monitoring measures, millions of patients are at risk for unforeseen complications, potentially costing our already overburdened healthcare system billions of dollars.

With off-label drug use accounting for 21% of prescriptions,[2] and even higher rates in pediatrics (62%),[3] relying on shortened and smaller clinical trials increases the risk to all patients and consumers, whether the drugs are later approved for broader indications or not. Most off-label prescriptions are based on poor or no scientific support. A 2011 report from the Agency for Healthcare Research and Quality determined that atypical antipsychotics are frequently prescribed for off-label uses and that many of the most common off-label uses, such as substance abuse and ADHD, have no clinical data to support their use.[4] Moreover, despite a black box warning about high death rates when used by elderly patients, research indicates that 9% of nursing home patients continue to receive these drugs.[5] Despite billions of dollars in fines to America's largest pharmaceutical companies for kickbacks and illegal promotion of atypical antipsychotic drugs, and despite enormous media attention to inappropriate and over prescribing of antipsychotics to foster children, nursing home patients, and other vulnerable populations, the FDA has been unsuccessful in protecting these or other patients and these drugs continue to be the most widely prescribed in the U.S.[4]

Since 2004, there have been 28 settlements with drug companies over promotion of drugs for unapproved use, with many cases targeting patient populations in whom these drugs have never been tested. In addition to billions of dollars in fines, these cases have resulted in billions of dollars in fraudulent Medicaid and Medicare claims. Major fines in 2012 against GlaxoSmithKlein, Johnson & Johnson, and Amgen prove that misbranding and illegal promotion continues to be a problem. In many of these cases, an initial FDA approval for use in a limited population was successfully used to market a drug to a broader population. The FDA has not developed effective strategies to stop this.

The situation is even more difficult now that the U.S. Court of Appeals for the Second Circuit determined that pharmaceutical representatives can promote off-label use under the First Amendment.[6] The FDA has not challenged that ruling, which could weaken the FDA's already limited ability to protect patients from drugs being promoted for off-label use.

Reliance on insurance and post-market studies will not protect patients from risks of using misbranded drugs. Patients need to be warned about the limited population approval before choosing to use one of these drugs.

Lack of insurance reimbursements for off-label use will not be an adequate deterrent. Many Americans currently do not have prescription drug coverage, and many physicians and patients will be willing to prescribe and pay for drugs that they assume are safe and effective since they are FDA approved. Patients are often unaware that they are taking a drug for an unapproved use, and many physicians do not fully understand the risks inherent in off-label use.[7] A label change does not provide sufficient information for a patient to understand if a drug approved for a limited population will benefit them. Approval of drugs for limited populations will only shift the burden of proving safety and benefit to patients, who will be unwitting guinea pigs.

In conclusion, the proposed new pathway represents a vaguely worded and dangerous plan. There is no clear evidence that the new pathway would be any better than—or even as good as—any existing pathway. In

contrast, the risks are clear that patients can be harmed if the FDA approves new drugs based on smaller, shorter-term studies using surrogate endpoints that are not patient-centered. For those reasons, we urge the FDA not to implement this drug approval pathway.

American Medical Student's Association
American Medical Women's Association
Annie Appleseed Project
Breast Cancer Action
Connecticut Center For Patient Safety
Consumers Union
Jacobs Institute of Women's Health
National Physicians Alliance
National Research Center for Women & Families
National Women's Health Network
Our Bodies Ourselves
TMJ Association
Union of Concerned Scientists
U.S. PIRG

For more information, contact Paul Brown at pb@center4research.org or Jennifer Yttri at jy@center4research.org or (202) 223-4000.

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[1] PCAST report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation, 2012 http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

[2] LePendu, P. et al. Analyzing patterns of drug use in clinical notes for patient safety. *AMIA Summits Transl Sci Proc*. 2012

[3] Bazzzano, A. et al. Off-label prescribing to children in the United States outpatient setting. *Acad Pediatr*. 2009.

[4] Maher, A. and Theodore, G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. *J Manag Care Phar.* 2012.

[5] Dorsey E.R, et al. Impact of FDA black box advisory on antipsychotic medication use. *Arch Inter Med*. 2010.

[6] United States v. Caronia. Docket No. 09-5006-cr (2nd Cir. 2012).

[7] Chen, D.T. et al. U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidemiol Drug Saf.* 2009.