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Dear Ms. Taylor:

On behalf of the American Society of Nephrology (ASN), thank you for the opportunity to comment on the American College of Physicians' (ACP's) draft policy monograph, "Improving FDA's Regulation of Prescription Drugs." ASN is a not-for-profit organization of 11,000 physicians and scientists dedicated to the study of nephrology and committed to providing a forum for the promulgation of information regarding the latest research and clinical findings on kidney diseases. ASN commends ACP for a thoughtful discussion of current deficiencies with the US Food and Drug Administration's (FDA's) system of regulatory control; however, the Society has a number of recommendations for ways to enhance the document and the recommendations. For the purposes of clarity, ASN's comments begin with broad suggestions and progress into comments pertaining to specific aspects of the recommendations.

ASN agrees that FDA is facing significant challenges with the current budget environment and system for clinical trial and drug review. However, ASN encourages ACP to include language in the document's executive summary as well as the background information (page 1 and 2) that highlights the positive work of the FDA, with particular attention to the dedication and expertise of FDA's scientific workforce. As many of the problems at FDA pertain to restricted funding, ASN wants to recognize FDA staff for their hard work and effort to ensure the safety of America's drug supply in light of current budgetary constraints.

Funding

ASN encourages ACP to expand on the issue of chronic underfunding. In its background discussion, ACP touches upon the "severe under-funding" that "restricts FDA's ability to monitor the safety and efficacy of new drugs once they're approved." However, chronic under-funding impacts all aspects of current FDA regulation while the expanded authority recommended in the monograph will likely require a significant increase in the FDA budget beyond what is already needed. ASN recommends ACP address these concerns about the FDA budget, both in the background discussion and within the recommendations. In particular, ASN suggests ACP create a recommendation that solely addresses the need for increased funding via the direct appropriation. As it currently stands, Recommendation 1 includes so many issues that funding is lost in the argument.

According to the FDA Science Board report, "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," published November 2007, the FDA is in a "precarious position" due to chronic underfunding caused by an insufficient increase in funds proportionate to increased responsibility and demands on the agency. In the study of FDA's needs related to scientific expertise and technology, the Science Board found that "gaps [in scientific expertise] were so intertwined with two decades of inadequate funding that it was impossible to assess technology without also assessing resources."

In spite of these assessments, President George W. Bush's fiscal year 2009 budget proposal, if passed, represents an additional year of inadequate funding. William Hubbard, former Deputy Commissioner at FDA and spokesperson for the Alliance for a Stronger FDA, calls it "barely half of what FDA needs just to keep pace with inflation...This proposed budget would likely force the agency into further staff decreases, at a time when it is urgent to increase staff." While not proposing ACP include a specific budget request in the policy monograph, ASN believes a general imploration for increased funding will benefit the agency and add merit to the following recommendations.

Pre-approval Process

ASN appreciates the overview of deficiencies in the preapproval process described in the monograph's background section. However, the Society is concerned with the apparent contradiction between the problems identified in the torcetrapib-Lipitor example and the assessment in Recommendation 1 that the pre-approval process is "well-defined" and "robust" and that more attention and funding need to be given to the post-marketing phase.

ASN supports some expansion of FDA authority to ensure drug effectiveness and safety. However, given ACP's second recommendation to expand FDA's regulatory authority in pre-approval trial design, ASN is worried that a declaration to "balance" resources between the pre- and post-approval phases may lead to an unfortunate decline in pre-approval funds at a time when increased support is actually being advocated.

ASN is also concerned that pharmaceutical company influence—due to their significant contributions in the way of user fees—may impact FDA's ability to exercise objective regulatory authority. One suggestion for combating potential pressure is to create an independent board of external scientific experts, free of any conflicts of interest, to assess trial design and make recommendations to FDA for improvement. In turn, the agency would have regulatory power to enforce the recommended changes.

In addition to *who* controls clinical trial regulation, ASN has some apprehension about the structure of clinical trial design. According to the monograph, "the present system is highly focused on rapid approval of new drugs and reducing delays in the availability of new therapies," thus leading to the recommendation to increase patient sample size and length of study. However, recent reviews of the FDA prescription drug approval process present differing analysis. The Government Accountability Office (GAO) found in 2006 that the timeline for drug discovery, development, and review is too long. GAO recommended *shortening* the review process for diseases with the most need for treatment, using a conditional approval mechanism to assure safety.

ASN is cautious to support recommendations that extend the length of time for novel therapies to reach patients in need. In 2006, 47 new drugs were approved by FDA, and only 18 were new molecular entities (those drugs considered most likely to treat diseases that kill the most patients). ASN would rather support conditional approval mechanisms, as touched upon in Recommendation 3 (page 5, lines 31-42), than lengthening trial time, and suggests moving this discussion to Recommendation 2.

An area where ASN believes FDA must improve clinical trial design is patient representation. ASN recommends including a requirement in Recommendation 2 to design clinical trials with appropriate participation from patients of unique populations (page 4, line 39). The National Institutes of Health (NIH) grant application contains a requirement to include women, minorities, and children in research, but the FDA has no similar requirement for clinical trial design. According to Gregory P. Geba, MD, MPH, Vice President of US Clinical Development and Medical Affairs at Novartis Pharmaceuticals Corporation, "patient characteristics are often associated with markers of disease prevalence and severity *and*

influence how an individual absorbs, metabolizes, and ultimately responds to medications designed to treat that disease.”

Post-marketing Testing

ASN agrees that FDA must devote additional attention to post-marketing review, particularly considering recent controversies. Members of ASN have expressed concern that there is insufficient education for physicians when it comes to the Adverse Event Reporting System (AERS). In anecdotal discussions, it is apparent that many physicians do not report adverse events to FDA on their own patients. FDA should improve its education of physicians on how and when to report an event that is potentially drug related. There may also be a role for subspecialty societies in liaising with the FDA to coordinate and facilitate education for their memberships.

While supportive of a clinical trial database, ASN has a number of questions on the logistics related to a publicly accessible databank of pre-approval and post-marketing clinical trials. In particular, while ACP raises the lack of compliance required for ClinicalTrials.gov as a deficiency with the program, there is no requirement for company compliance under Recommendation 4a. In addition, to assure “full public disclosure of clinical trial results,” FDA must have some mechanism for data review and authority to require additional disclosure if necessary.

ASN is also unsure of the proposed databank’s interaction with ClinicalTrials.gov. Is the databank an extension of the current website or is it meant to be a separate entity? Will FDA and/or NIH serve as the databank controller or will the agency contract with a not-for-profit organization as suggested on page 6, line 24?

Foreign Drug Manufacturing

ASN agrees that recent crises highlight the need for increased FDA oversight of foreign manufacturers and their facilities. While ACP effectively describes the controversy and outlines Representative John Dingell’s draft legislation, the monograph would benefit from a more definitive recommendation. Does ACP support additional user fees on imported food and drugs to fund foreign drug inspection? What technological improvements are required to resolve FDA’s “flawed and inaccurate databases?” Is legislation required to provide FDA with the authority to conduct unannounced foreign inspections? ASN supports legislation that provides FDA with the necessary resources to regulate foreign drugs as thoroughly as domestically-manufactured pharmaceuticals.

Thank you for considering ASN’s comments on FDA’s regulation of prescription drugs. Please contact ASN Director of Policy and Public Affairs Paul C. Smedberg at (202) 416-0646 or psmedberg@asn-online.org, with questions or comments about this letter.

Sincerely,



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President

cc: Sharon Adler, MD
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