Public Comment

Joan Grobstein, M.D.

There are so many issues that need to be addressed by CFSAC at this time that it is hard to know where to begin. Most of these issues have been raised by patients at many previous meetings, but there has been little improvement in ME patients' lives despite numerous strong recommendations by this Committee.

I have no desire to focus on the negative, but there is very little progress on which to focus. At the FDA meeting we were told to go to our legislators, fund our own foundations, take care of ourselves. This patient population cannot do that. We are citizens, and we have the same patients' rights as the rest of the population. Yet, because of the CDC's ill-conceived definition and refusal to do needed studies and education, doctors know little about our disease and have a CDC mandate to do no testing. Underlying or co-existing infections and conditions are not identified or treated. Orthostatic intolerance is ignored. Immune dysfunction is not taken into consideration. Cognitive dysfunction is not recognized. Sleep disorders are ignored.

I will organize my remarks by agency.

FDA

I very much appreciate the time, energy and commitment that was demonstrated by the FDA at the recent Meeting and Workshop held on April 25 and 26. Many important issues were raised and discussed, and I think there is a new level of understanding of ME and CFS at the FDA as a result.

However, there is, as yet, no visible positive outcome for patients: no new drugs in the pipeline, no evidence that old drugs are being re-purposed, no statement on which already-existing biomarkers (vO2 max, NK cell function, gene expression testing) are acceptable as outcome measures in drug trials, and no official FDA recognition of the Canadian Consensus definition as the appropriate tool for determining patient groups for drug trials. In the presentation on outcome measures every outcome measure currently being used in ME were questioned; even the SF-36 (an outcome measure that has been used in many diseases for years) was said to be inadequate in ME and CFS. The impression that was given to the few drug company representatives that attended is that there are no good outcome measures in this disease. This is a devastating message to the future of pharma-funded therapeutic trials for ME.

During one of the breaks, I asked Dr. Kweder if vO2 max is a biomarker. She replied that it is. Why are NIH and FDA not collaborating to make sure that the research to validate vO2 max as a biomarker for ME is done and done quickly? The pharmaceutical companies will move rapidly to repurpose drugs and develop new ones if they know they have the tools to demonstrate efficacy.

There was not much discussion of safety. It's important to continue to note that the side effects of many medications are similar to the symptoms of ME, and also to note that patients are so sick they are willing to tolerate significant side effects in exchange for relatively small improvements in functionality.

I have been told that FDA and NIH collaborated at the beginning of the AIDS epidemic to speed drug development. I am too sick to research how this was done within the procedures of each agency. **Dr. Michele is clearly the person to identify how FDA and NIH cooperated to make progress in AIDS and create a similar path for drug development for ME.** This plan should be presented at the next CFSAC meeting.

I would like to note here that it is not correct that there was no biomarker for AIDS. The earliest biomarker for AIDS was, unfortunately, death. As the epidemic progressed other biomarkers were developed that could serve as surrogate endpoints. **It is very likely that vO2 max is the biomarker for ME. A study to validate the findings of the Pacific Fatigue Lab should be funded and initiated immediately.**

NIH

The first goal of the NIH should be to validate biomarkers for Canadian Consensus-defined ME. Funding for this should be made available immediately, because this is an urgent matter. At this time, the most likely candidates are vO2 max, pre- and post-exercise gene expression as demonstrated by the Lights, and NK cell function. With adequate funding it should be possible to validate one or more of these markers within 12 to 24 months. This is the highest priority.

One of issues that was raised repeatedly at the FDA meetings and which has also been raised many times at previous CFSAC meetings is the need for a clinical trials network. Dr. Dimitrakoff has mentioned the example of MAPP for pelvic pain. He has pointed out the availability of RU-34 grants for the planning and development of such a network for ME. There are several research groups already working on ME in the US which are obvious candidates for such a network. **Dr. Maier should explain the procedure for obtaining an RU-34 grant for Canadian Consensus-defined ME and should be actively involved in making sure that it gets awarded on an expedited basis.**

It could be questioned whether the Canadian/International definition is the best definition for ME. This is already obvious to many patients, because we live the disease, and it is clear which definitions describe us and which do not. Fukuda is not a good definition, because it is overly inclusive and has resulted in the current confusion in the research literature. NIH is apparently currently involved in a process to clarify the definition, but we have no information about this process, even its timeline. Scientists have made big mistakes about this patient population in the past (witness Fukuda). **Informed patients and ME experts must be involved in any process related to the definition.** In addition, there are at least two other definition processes in progress: the CDC is doing a 7 center study with the probable aim of creating a new definition or "evolving" an old one, and CFSAC has recommended that it has its own workshop on the definition. The three efforts are independent, so there is a high probability that, at the end of the

day, there will be more confusion rather than less. It would be best to **stop all three efforts and initiate a single process with CDC, NIH, CFSAC, and, most importantly, informed patient and ME expert involvement.**

I applaud the creation of the trans-NIH Working Group on ME/CFS. However, its proceedings are completely opaque. There must be informed patient participation and transparency.

Finally, **NIH must make funding available that is specifically dedicated to ME and CFS and is commensurate with the burden of disease.** There are many needs: biomarker validation and discovery, basic pathophysiology with special focus on post-exertional malaise, the role of multiple, often concurrent infections including viruses and tick-borne pathogens, creation of centers of expertise for patient care and provider education, evaluation of potential therapeutic agents, identification of the location of housebound patients and creation of a care model for them, evaluation of long-term outcomes, a further understanding of co-existing conditions, etc. The list is long, and $6-10 million per year is not sufficient to make a dent in our scientific ignorance.

CDC

It is remarkable that the CDC 7 center study has been going on for several months, yet they do not appear to have measured the most likely biomarkers for ME: vO2 max, NK cell function, and pre- and post-exercise gene expression. After 25 years, we do not need more descriptive data. The Canadian and International definitions define this patient population well. **The 7 center study should be stopped, and informed patients and ME experts should be involved in the design of any further research on ME at CDC.**

With the help of informed patients and ME experts, CDC must do the epidemiological research that is the agency's responsibility: longitudinal studies, and in-depth studies of geographic and family clusters. It is clear that ME sometimes occurs in several people who live or word together. The key to its etiology may lie in this fact; cluster must be adequately studied.

CDC currently has no meaningful dialogue with informed patients. PCOCA calls give us old information which we already know. There is no dialogue. Patients are asked to submit questions in advance, but the questions are not answered. Dr. Unger answered only one question during the last PCOCA: about flu shots, not a substantive question about CDC's scientific endeavors.

CFSAC

Patient attendance at CFSAC is likely to be quite sparse in May, 2013. Many patients are still recovering from attending the FDA meetings, submitting testimony, or merely from watching it. It is important that the members of the Committee attend to that reality. Please do not assume

that the sparse attendance is evidence of lack of interest. It is also important to note that attending a 2 day meeting is devastating to many patients.

There are still many procedural problems at CFSAC. The agenda was not available 2 weeks prior to the meeting, as promised. There is little information on the agenda: speakers are not named; it's unclear what time public testimony will be given, so patients cannot plan their trips to Washington accordingly; one of the agreed-upon agenda items for this meeting was prioritizing past recommendations (so many of which have not been acted upon in any substantive way), yet this item does not appear; there is no designated time for committee reports, which has been a problem at previous meetings; the talks which are scheduled do not address patients' most pressing needs. CFSAC is also not making reasonable accommodation for patients' disabilities: the scheduling issue has already been mentioned, and requests for accommodations for orthostasis are denied.

However, the overriding concern about CFSAC is that it is ineffective. Good recommendations are made but are ignored by the agencies. We have attempted to contact the agencies outside of CFSAC and have been told by HHS that CFSAC is our only avenue to communicate with the government. This is not acceptable, because we are making no progress toward improvement in patients' lives. Many patients no longer believe that CFSAC is likely to be of any help to them. We need a better forum for a dialogue with our government.

We need a strategic plan for ME and CFS. Dr. Lee has said that HHS no longer wants to make strategic plans, yet we see that they exist for other diseases. We have been told that CFSAC is our only mode of communication, yet FDA was willing to arrange a two day meeting. We are tired of being misled. I suggest that a special forum be convened before the next scheduled CFSAC in November, including all of the relevant agencies, our ME experts and patients. We must move forward.