Dr. Jennifer Furin, Harvard Medical School, Department of Global Health and Social Medicine

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First, I would like to thank the members of the FDA review panel for allowing me to speak with you today. I come to you in my capacity as an MDR-TB clinician with 25 years of experience treating this disease all over the world. In fact, MDR-TB was the first disease I ever treated when I began as an enthusiastic first-year medical student working in the slums of Lima, Peru back in 1995. And in this way, MDR-TB is forever linked with the foundation of medical science and practice for me.

I have personally witnessed untold suffering experienced by thousands of persons with MDR-TB. Much of their suffering was due to the treatment regimens they received, which were not rigorously assessed, were long and highly toxic and, in all truth, were not that effective. Our fellow humans with MDR-TB are desperate for shorter, safer and more effective therapeutic regimens. And we, their providers—as you have no doubt read in many of the public comments—are desperate to provide that kind of treatment for them. Our dreams are big. Why not a one month regimen? Why not a 1 week regimen with one pill? These are our aspirations but wishing for them does not make them so. And, in fact, as I learned that same first year of medical school, we can become blinded by desperation and more prone to making errors.

Because the stakes are so high, the field of medicine has developed tools to protect the safety of those in our care. All members of the medical team have a crucial role to play in this, and as a stringent regulatory authority, so too does the FDA. So I would invite you to

take part in a practice that has been developed in the field of medicine known as the "time out". It is precisely when we are engaged with the heady promises of potential that we must ensure we do not overlook the basics. The time out is a mindful pause that not only protects patients but also protects all individuals involved in the life and death decisions that are part of medical care.

During this "time out" I would ask the FDA panel members to consider 5 issues that are core components in the evaluation of the novel chemical entity pretomanid for MDR- and XDR-TB. These are:

1) The current context of treatment for MDR-TB and XDR-TB. Using the 50% historical success rate to assess the efficacy of the NIX regimen is setting the bar too low. It was based on cohorts treated before 2012 and excluded patients who received BDQ, LZD or DLM. The landscape for treating MDR and XDR-TB has radically changed since 2012, and the use of BDQ and LZD has led to cure rates above 80% in multiple cohorts. While taking the unusual step of considering approval of a novel chemical entity which was assessed in a small population without the benefits of contemporary control groups, relying on historical data from 2012 and from people who did not receive BDQ and/or LZD is misleading.

2) The evidence that is available on the effectiveness of pretomanid. The FDA briefing documents notes that "the efficacy conclusions depended on whether 50% was a reasonable benchmark." I would suggest it is not. Excellent treatment outcomes with >80% success have been recorded among cohorts of patients who received bedaquiline and linezolid without the benefit of pretomanid. While appreciating the need for testing whole regimens

in MDR-TB, this can and is being done with adequate control groups to better elucidate the role played by individuals drugs.

3) The safety of pretomanid, especially with regards to liver toxicity and testicular toxicity. The cessation of the STAND trial due to several cases of fulminant hepatitis, some of which ended in death, is cause for concern. The numbers of persons who developed elevations in the liver transaminases in NIX-TB reported to the public have varied as well. The FDA is the only agency to have all the safety data on pretomanid and in this way your role on the medical team is one that cannot be fulfilled by any others.

4) The safety of the NIX-TB regimen as a whole. High rates of toxicity to linezolid were reported in the NIX-TB study so much so that a change in the dosing regimen was made during the execution of the protocol and future studies—including some being done by the sponsor submitting this pretomanid application –are underway to better elucidate how to administer linezolid in a safe and effective manner.

5) The impact of pretomanid approval on the field of MDR-TB clinical science. MDR-TB trials are a nascent but growing field, and the best evidence comes from randomized, controlled trials. If a novel chemical entity can be approved by the FDA without appropriate controls, what would be the impetus of including such controls in future trials? How could we ask participants to be part of such studies if new drugs can be approved without them?

In closing, I thank the members of the advisory panel for taking this short "time out" with me. All of us working in the field of MDR-TB are in complete agreement that we are badly in need of new drugs and shorter regimens. But we are also badly in need of solid science

to support the care of individuals living with this disease. Are we convinced the best science was used and the best data available to approve the novel chemical entity pretomanid? The FDA as a stringent regulatory authority has a unique role to play in answering that question, and as we all engage in this serious business of life and death, I have one humble request of you all. Please be stringent.