UNITED STATES – CONTINUED SUSPENSION OF CONCESSIONS IN THE *EC – HORMONES* DISPUTE

EXECUTIVE SUMMARY OF THE ORAL STATEMENT OF THE UNITED STATES ON EXPERT ISSUES AT THE SECOND SUBSTANTIVE MEETING OF THE PANEL

October 13, 2006

1. The United States has repeatedly argued throughout these proceedings that the European Communities' ("EC") permanent ban on estradiol 17β ("estradiol") is not based on a risk assessment within the meaning of Article 5.1 of the *Agreement on the Application of Sanitary and Phytosanitary Measures* ("SPS Agreement"). We have also argued that the EC's provisional bans on progesterone, testosterone, zeranol, trenbolone acetate ("TBA"), and melengestrol acetate ("MGA") do not satisfy the necessary conditions for a provisional measure within the meaning of Article 5.7 of the SPS Agreement. Indeed, the very conclusions underpinning the EC's decision-making are unsupported by the scientific evidence relating to these hormones. The experts' written responses and oral testimony support these U.S. arguments.

2. At the outset of this meeting, it is essential to recall the purpose of last week's meetings and today's discussions. The World Trade Organization ("WTO") and this Panel are not being called upon to conduct a risk assessment for the EC. You have not been requested to provide or complete a *de novo* review of the numerous scientific materials relating to the six hormones at issue. The pertinent analysis, as discussed a moment ago, is what the EC has done. Not what the EC could have done, or may still do. Not what this Panel can do for the EC. To conduct an analysis of what the EC has actually done, we may ask much less complex questions such as: has the EC presented scientific evidence of a risk from these hormones when consumed as residues in meat and assessed this risk in the proper fashion?

3. As I will highlight this morning, the experts' responses confirm that the EC has not based on a risk assessment its ban on meat from cattle treated with estradiol for growth promotion purposes. It has not satisfied the four necessary steps for a risk assessment, and several of the conclusions set out in the EC's Opinions are not supported by scientific evidence. A measure banning meat from cattle treated with estradiol cannot be "sufficiently warranted" or "reasonably supported" by this absence of a risk or assessment of the risk.

4. Likewise, the experts' responses confirm that there is sufficient scientific evidence to complete a risk assessment for each of the five "provisionally banned" hormones and that the EC has not based its provisional bans on available pertinent information. In other words, the EC's measures and "risk assessment" do not satisfy its obligations under the SPS Agreement.

5. I think that a brief discussion of the term <u>zero risk</u> provides a good starting point for today's discussions. It is an important principle and one to which the EC referred several times in the meeting with the experts. Indeed, the EC at several points asked the experts whether they could ensure that there was "zero risk" of a certain event occurring. The EC used this same tactic in its written comments on the experts' answers. For example, it demanded that <u>Dr.</u>

Boobis "provide the necessary assurance" to the EC that residues in meat will never be shown to pose a risk to consumers. (*See*, *e.g.*, EC Comments on Question 20).

6. The analysis must refocus on the question of whether the EC has provided any evidence of a risk. The relevant discussion is one of whether the EC, in support of its ban, has adduced sufficient evidence to demonstrate a risk from meat from cattle treated with estradiol for growth promotion purposes. Included in this discussion is an analysis of whether the EC has provided scientific evidence that estradiol is genotoxic, mutagenic or carcinogenic (at levels found in residues in meat from treated cattle). Whether a scientist refuses to commit to a stance that there will never be a risk from meat treated with estradiol at some point in the future is not pertinent to this analysis because it is not scientific evidence of a risk. It is simply theoretical uncertainty and cannot be the basis for a risk assessment or an SPS measure.

7. Regarding what, exactly, makes up a risk assessment, the experts and international organizations reiterated the four steps of risk assessment. In addition, the Codex representative stressed that a risk assessment must be based on all available data.

8. As to whether and when a risk assessment must satisfy each of the four steps, there was clear agreement among Drs. Boobis and Boisseau and JECFA that an evaluation of the human food safety of a drug should include all four steps of risk assessment. JECFA noted that a hazard identification does not qualify as a risk assessment and that the assessment should continue through each of the four steps unless there is "clear cut" evidence, both *in vitro* and *in vivo*, of genotoxicity. Dr. Boobis commented that the only instance in which such an assessment would stop at the hazard identification stage would be if the compound were identified as a DNA-reactive mutagen. Dr. Boisseau confirmed Dr. Boobis' opinion.

9. Recall that, as we learned last week, genotoxicity and mutagenicity are not synonymous. Genotoxic substances damage DNA but the damage may be repaired. If the damage results in a mutation and the cell divides, then the substance is a "mutagen." As will be discussed in a moment, the experts did not identify any scientific evidence in the EC's Opinions that confirms, *in vivo*, the effects of estradiol at levels below those causing a hormonal response, let alone any evidence that effects at that level are those of a DNA-reactive mutagen.

10. There are four steps for a risk assessment that have been clearly defined by the experts and the original *Hormones* panel. And the EC accepts that these four steps are required. As just mentioned, a risk assessment for estradiol may not stop at the first step of hazard identification unless there is *in vivo*-confirmed evidence that estradiol is either a genotoxin or a DNA-reactive mutagen. The EC has failed to present any evidence that estradiol is genotoxic at levels below those eliciting a hormonal response, nor has it provided evidence that estradiol is mutagenic at relevant levels *in vivo*. The EC was therefore not justified in failing to complete the three remaining steps.

11. The experts confirmed that the EC did not complete the remaining steps. Dr. Boobis noted, and Dr. Boisseau agreed, that the EC's Opinions are focused on the first step of risk assessment, hazard identification. As noted by JECFA, a hazard identification does not equal a

risk assessment. An assessor must finish all four steps. Although he did not speak on this subject in last week's meetings, Dr. Guttenplan has described the EC materials as deserving at best a "mixed rating" in terms of the four steps of risk assessment. (Question 14). He noted particular deficiencies in the hazard characterization and risk characterization sections. (Questions 13 and 14).

12. Another avenue for finding that the EC has not completed a risk assessment for estradiol is by determining that the conclusions set out in its assessment are not supported by scientific evidence. For example, the experts agree that the EC has not presented any scientific evidence that estradiol is genotoxic *in vitro* or *in vivo* at physiological levels. The normal action of estradiol on a cell is mediated through the estrogen receptor. The genotoxic effects, which are abnormal, are not mediated through the estrogen receptor but instead involve direct damage to DNA. To date, concentrations of estradiol required to cause genotoxic effects have been well above those required to elicit normal physiological effects.

13. As noted by Dr. Boobis, positive *in vitro* tests require positive *in vivo* confirmation, as toxicity is not always expressed *in vivo*. For Dr. Boobis, *in vivo* confirmation is critical because, among other things, it takes into account DNA repair mechanisms. He commented that he was "not persuaded" that estradiol is genotoxic at levels below the normal hormonal concentrations present *in vivo*. In other words, that the genotoxicity has a threshold that requires overwhelming the DNA repair mechanisms – an event that will only occur at concentrations well beyond physiological levels.

14. The experts could not identify any studies providing evidence of the *in vivo* confirmation of genotoxicity of estradiol at levels below those required to elicit a hormonal response. When put on the spot at last week's meetings with a new study produced by the EC in a last minute attempt to provide evidence of *in vivo* effects, Dr. Boobis quickly dismissed the study as irrelevant. The study's authors had treated the subject rats with so much estradiol that the sheer level of the dose itself killed fifty percent of them, precluding any interpretation of estradiol-specific effects.

15. Another example of an unsupported conclusion in the EC's Opinions is that estradiol residues in meat from treated cattle are carcinogenic. The EC has failed to present any scientific evidence that estradiol will have carcinogenic effects at levels found in residues in meat from treated cattle. Their failure to provide any evidence makes abundant sense. We consume estradiol residues from numerous sources every day at levels much greater than those found in meat residues, whether from cattle treated for growth promotion or not. Milk, butter, eggs and, as noted by Dr. Boobis, a great number of phytoestrogens in plant products are all sources of estrogen in our diets.

16. The EC has failed to support either of these major conclusions on genotoxicity or carcinogenicity with scientific evidence. The SPS Agreement does not permit the EC to do so. An assessment that fails to adduce scientific evidence in support of its underlying conclusions is not a risk assessment, as appropriate to the circumstances, under SPS Article 5.1.

17. There is a similarly uncomplicated analysis by which it can be determined that the EC's "provisional bans" do not satisfy the requirements of SPS Article 5.7. The first of Article 5.7's requirements for a provisional ban is that the evidence be insufficient to conduct a risk assessment. None of the experts believes that this is the case for testosterone, progesterone, zeranol, TBA or MGA

18. Since the experts have confirmed that the evidence for each of the five hormones is sufficient to complete a risk assessment, discussion of the "provisional" bans may stop here in light of the cumulative nature of Article 5.7's requirements. The EC's ban is not a provisional measure for purposes of the SPS Agreement.

19. The second of Article 5.7's requirements is that a provisional measure be maintained on the basis of available pertinent information. The EC's "provisional" bans do not satisfy this requirement because there is no available pertinent information indicating that any of the five hormones poses a risk to consumers when used as a growth promoter in cattle.

20. The views of the experts are evidence of a lack of available pertinent information indicating that the five hormones pose a risk when consumed as residues in meat. Indeed, all available pertinent information indicates that consumption of these residues is safe. The EC has therefore not based its "provisional" bans on available pertinent information within the meaning of SPS Article 5.7.

21. In light of the experts' responses, it is clear that the EC has neither based its permanent ban on estradiol on a risk assessment nor developed legitimate provisional bans. An analysis of these points would not entail the type of *de novo* review to which I alluded earlier. As noted, none of us are equipped for such a review and the SPS Agreement does not require or condone such a review.

22. While the Panel's analysis need not extend to this issue, I will now take a moment to discuss the EC's arguments relating to prepubertal children. The EC claims that estradiol residues in meat from treated cattle pose a risk to this sub-population. However, the EC fails to provide scientific evidence of this risk.

23. In particular, the EC relies on an assay that, to date, remains unvalidated; the EC has failed to produce any scientific evidence demonstrating that JECFA's ADIs do not sufficiently protect children; and the EC has failed to complete the necessary steps of a risk assessment for this population.

24. This does not mean that the doubts and theoretical uncertainty on circulating estradiol levels in prepubertal children identified in last week's meetings are unimportant. They are important. Indeed, JECFA reaffirmed that ensuring the safety of children is a "basic principle" of risk assessment and a fundamental focus of its work. As such, it is a safe guess that JECFA would be interested in any new evidence relating to this sub-population. As we have learned from the JECFA and Codex representatives, however, the EC has not shared any information with them. If the EC believes that the information it possesses has been properly validated and that the evidence is sound, then every Codex member around the world would benefit from its

conclusions. The EC is not alone in its desire to protect the health of prepubertal children and other sensitive sub-populations.

25. Finally, we come to the issue of misuse of growth promoting hormones in the United States. I have left this subject for last because, quite frankly, it is unclear what role misuse plays in the EC's Opinions and arguments. The EC apparently considers potential misuse to be a risk, but has failed to provide any evidence or argument as to how it has actually assessed this risk. It provides no evaluation of the actual system of controls in place in the United States. We have described these controls at length in our previous submissions to the Panel. Dr. De Brabander claimed to have examined the U.S. system of controls when he opined that the U.S. system is nothing but "audits and paper work." However, he provided no analysis of the actual U.S. system. Neither did the EC. In fact, when asked in last week's meetings whether he was familiar with the U.S. and Canadian meat safety systems, Dr. De Brabander noted that he was not a meat inspector and was not qualified to make judgments on these systems.

26. Even if one were to assume the unrealistic and hypothetical misuse scenarios developed by the EC, the EC has failed to present convincing evidence that misuse leads to violative residue levels.

27. Finally, the EC fails to assess the risk of misuse. While the experts did not have a chance to turn to this point last week, the necessary evidence of the EC's failure may be found in their written responses. (*See, e.g.,* the responses of Drs. Boobis and Boisseau to Question 48).

28. When you take a step back from the EC's Opinions, it becomes more and more clear that they are flawed in larger ways than the EC would like us to see or focus on. In light of its line of questioning to the experts last week, the EC apparently hopes to make this dispute one about getting lost in the weeds of several scientific dead-ends. The specters of misuse, risks to sensitive populations and the unwillingness of the experts to commit to a position that there will never be evidence of a risk from any of these hormones in the future are examples of these scientifically unfounded pitfalls. We could go on *ad nauseam* in a debate as to whether science in these areas is evolving. As we know from our discussions with the experts last week, science is continually evolving. This evolution cannot be equated with evidence of a risk, however. We are not scientists, and an attempt to thrust ourselves into the debates on these issues would be nothing more than a misguided *de novo* review of the science by us, laypersons.

29. If we follow the paths laid out by the EC, we will lose sight of the larger problems of the EC's Opinions and the fundamental obligations and requirements against which they are to be measured – those set out in the SPS Agreement. When we view the EC's measures in this context – in which we have the necessary knowledge and can perform the necessary analysis – it is clear that there are several avenues by which we can conclude that the EC has not based its permanent ban on estradiol on a risk assessment within the meaning of SPS Article 5.1, nor has it implemented a provisional ban on the other five hormones within the meaning of SPS Article 5.7. I have discussed these avenues and the appropriate conclusions that can be reached for each based on the scientific record in this dispute this morning.