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**RE: Disclosure Timing**

Dear Dr. Sim:

Merck appreciates the opportunity to comment on the timing of data disclosure.

Merck is committed to registering all Phase II, III, and post-marketing controlled clinical trials that we sponsor and conduct anywhere in the world, on ClinicalTrials.gov at study initiation. This commitment goes well beyond the current U.S. law mandating registration of clinical trials of products designed to treat life-threatening or otherwise serious illnesses, and beyond the industry commitment to register all “confirmatory” trials.

Merck believes that in some cases select, detailed information about a clinical trial protocol is sensitive for competitive reasons and it is neither necessary nor prudent to release such information at trial inception. The details of the study protocol are important for peer-review of a manuscript submitted for publication at trial completion, and Merck will readily provide the full protocol and amendments, data analysis plan, etc. to an editor, upon request, when a manuscript is submitted for publication. This is stated clearly in our publication guidelines for clinical trials, at [http://www.merck.com/mrl/swf/clinical\\_trial\\_publication\\_guidelines.swf](http://www.merck.com/mrl/swf/clinical_trial_publication_guidelines.swf)

For phase III studies, Merck will provide information on the 20 items identified by the WHO as the minimal data set for trial registration.

Merck’s phase II studies are designed to be hypothesis-testing, but they are not pivotal confirmatory trials, typically do not have clinically directive outcomes, and often are highly proprietary. For phase II studies, which Merck is voluntarily registering beyond the industry commitment to register all ‘confirmatory’ trials, Merck will provide information for the majority of the 20 data fields, consistent with the approach agreed

upon at the April 2005 scientific advisory meeting. The information provided for phase II studies is more than sufficient for patients to identify potentially appropriate trials for their disease conditions and pursue participation during trial enrollment. For these early phase studies, information that is potentially sensitive for competitive reasons includes:

- primary and secondary outcome measures,
- target sample size,
- full scientific title, and
- detailed information about the intervention such as molecular identity and duration.

This information adds little value for patients and physicians seeking to participate in a clinical trial. Note that later, if the compound under investigation enters phase III, Merck will update the registry entries for the earlier phase studies of the compound with the full information for the remaining fields. Again, Merck will readily provide the full protocol to an editor, upon request, when a manuscript is submitted for publication.

Merck's policy on the registration and publication of clinical trials is posted on Merck.com at:

[http://www.merck.com/mrl/swf/Merck\\_Position\\_on\\_Clinical\\_Trials\\_Registries.swf](http://www.merck.com/mrl/swf/Merck_Position_on_Clinical_Trials_Registries.swf)

Merck developed this policy after numerous internal and external discussions. We've made a concerted effort to fully assess our policies with the goal of making as much clinical trial information publicly available as soon as possible.

It is difficult to speculate on what might have happened, from a competitive standpoint, had certain specific information about a study protocol been publicly released early in clinical development. We understand there is much information in the public domain already. Competitive information is highly valuable and there are now companies that exist solely to pore over public information such as annual reports and posters from professional scientific meetings to assemble pharmaceutical pipeline information (and charge substantial fees to purchase such information). While much information is made publicly available by companies as part of scientific discourse and business communications, there is certainly additional information that remains confidential and may help a company retain a competitive edge in critical activities such as filing a patent application first, filing with a regulatory agency first, or bringing a product to market first.

One example where we feel that a subtle protocol detail was highly competitively sensitive involves the initial approval of Merck's leukotriene receptor antagonist SINGULAIR® (montelukast sodium) for once-daily treatment of asthma. In this situation, there was strong competition with another investigational once-a-day leukotriene receptor antagonist for which product would prevail in the market. Merck employed a novel strategic approach to determining optimal dose.

Protection against a bronchoconstricting challenge, such as exercise, is an important characteristic of asthma therapy. In these studies, Merck took the novel approach of performing the exercise challenge near the trough of the dosing interval. The bronchoprotective effects of leukotriene receptor antagonists had, to our knowledge, only

been studied at peak concentration. For the control of asthma, it was important to demonstrate efficacy near the end of the dosing interval for once-daily SINGULAIR. (As is our policy, the results of these clinical studies were submitted for publication in a timely fashion and are publicly available.<sup>1</sup>)

It is our firm belief that the completeness of the efficacy data in our FDA package, and the exceptional clinical profile of SINGULAIR including the novel approach to demonstrating efficacy of the dose near the end of the dose interval, led to regulatory approval in the U.S.

If these studies were starting now, and we were to register them and complete the primary outcome field, the information in the field would have to include “prevention of exercise-induced bronchoconstriction at the end of a once-daily dosing interval.” We believe that disclosure of this specific primary outcome information would have been damaging competitively.

Another example involves Merck’s new, once-weekly osteoporosis treatment, FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol). This is currently the only bisphosphonate with the added benefit of a weekly dose of vitamin D (vitamin D insufficiency is associated with reduced calcium absorption, bone loss and increased risk of fracture). In this case, disclosing the intervention and full scientific title would have given away the existence of the entire Fosamax+D program. One simply has to look at the name of the investigational product to have an understanding of the program and, we speculate, disclosure of our plans to develop this important new formulation could have led to competitors doing much the same thing.

In the original development of FOSAMAX® (alendronate sodium), in the early 1990s, Merck used novel biochemical markers of bone turnover with greatly improved assay precision in the early phase 2 studies, which allowed detection of a clear dose response, and comparability (metabolically) to the then-standard treatment for osteoporosis, hormone replacement therapy. This allowed us to make decisions about which doses to take into phase 3, and, we believe saved more than a year in development time. Merck disclosed this information later when the program was in phase 3.<sup>2</sup> Again, having to disclose the novel biochemical markers used as primary outcome measures at this early stage of development could have been competitively damaging.

Subsequently, several companies including Merck began working on once-weekly formulations of osteoporosis treatments. If any of the companies had a clear picture of the other's progress in developing once weekly or once monthly formulations vs. daily dosing, it would be a clear competitive advantage.

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<sup>1</sup> Reiss et al., *Thorax* 1997;52:1030-5. Bronsky et al. *Clin Pharmacol Ther* 1997;62:556-61. Leff et al. *N Engl J Med* 1998;339:147-52. Kemp et al., *J Pediatrics*. 1998; 133: 424-8.

<sup>2</sup> Gertz et al. *J Bone Miner Res* 1994;9:135-42.

We hope these sample cases help to illustrate the importance of select protocol details as competitive information.

We also want to express our concern with the limited involvement of the pharmaceutical and biotechnology industries in the November 2005 SAG meeting and hope that we and others will have the opportunity to participate in the April 2006 SAG meeting, and other discussions going forward. Following the April 2005 scientific advisory meeting in Geneva, we understood that WHO would convene a group to advise on this issue of delayed disclosure. It now appears that WHO plans to develop a delayed disclosure mechanism simply through open comment periods, with final sign-off by a SAG that does not fully represent all stakeholders. There are complex aspects to this issue that require a full WHO consultation process. For example, with regard to the time period for delay of information, it is simply not possible to prescribe a fixed time period. This will vary by the nature of each program, including the duration of the trial (e.g. weeks for treatment of depression; years for osteoporosis, etc.). Mechanisms for disclosure must address the security of the database information and establish clear roles and responsibilities of all parties involved, to prevent inadvertent or intentional premature disclosure. For the process to be successfully implemented, all stakeholders must be fully involved in the deliberations and the development of a balanced, sound system.

Thank you for your consideration of these comments. We look forward to continued dialogue with WHO and other stakeholders to promote transparency and allow patients and their healthcare providers access to clinical trial information, while preserving intellectual property protection.

Sincerely,

A handwritten signature in black ink, appearing to read "Theresa M. Wizemann". The signature is fluid and cursive, with the first name being the most prominent.

Theresa M. Wizemann, Ph.D.  
Director, Public Policy  
Merck Research Laboratories