OFFICE OF NEW DRUGS

Tertiary Review of Genetic Toxicology Studies Resulting in a Recommendation for a Clinical Hold or Conduct of Additional Studies

CONTENTS

PURPOSE

- This MAPP establishes policies and procedures in the Office of New Drugs (OND) for tertiary review of data from genetic toxicology studies. Tertiary review will occur when positive genetic toxicology study results serve as the basis for imposition of a full or partial clinical hold on an investigational new drug application (IND) or a request that additional studies be performed to further evaluate the positive findings. This MAPP also establishes a Genetic Toxicology Review Committee (GTRC) within OND to perform the tertiary review.

BACKGROUND

- ICH guidances S2A and S2B specify the genetic toxicology assays that should be performed and submitted in support of INDs and new drug applications (NDAs). Generally, a bacterial gene mutation assay (Ames test) and an in vitro mammalian cell assay for chromosome damage are performed prior to phase 1 clinical trials. The results of these assays are used to assess potential carcinogenic hazards.

- Positive results in genetic toxicology assays suggest that a candidate pharmaceutical has the capacity to activate oncogenes or disable tumor suppressor genes and could therefore pose a possible carcinogenic hazard. In many cases a positive result in a genetic toxicology test may lead to a decision by the review division director to impose a clinical hold (full or partial) on the IND (particularly with regard to repeat-dose clinical studies) and requests for additional studies to further explore the positive finding before additional clinical studies are allowed to proceed.

- The interpretation of genetic toxicology studies is not always straightforward. Occasionally statistical increases in genotoxicity endpoints are reported that may not be biologically relevant. This can occur when treatment values are statistically increased over concurrent control values but are still within the historical range of

control values for the particular assay. Artifactual results can also occur through excessive toxicity or extremes in culture conditions related to pH and osmolarity. Given the potential serious impact of a positive genetic toxicology test on the continuation of a development program for a drug and the potential implications to the safety of the administration of the drug to humans, it is critical that OND ensure that the review and interpretation of these studies occur in a consistent manner across the multiple review divisions. This approach will ensure that clinical division directors are provided with consistent, high-quality information about the genetic toxicology studies on which to base their decisions regarding the safety of allowing the proposed clinical studies to proceed. Further, this approach will ensure that OND recommendations and requests for additional studies to follow-up on a positive genetic toxicology study will be informed by the best available science in this area and will be consistent across review divisions.

REFERENCES

- ICH guidance for industry *S2A Genotoxicity: Guidance on Specific Aspects of Regulatory Tests for Pharmaceuticals* (61 FR 18198, April 24, 1996)
- ICH guidance for industry *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (62 FR 16026, November 21, 1997)

POLICY

- A GTRC will be formed to conduct a tertiary review of genetic toxicology studies that the pharmacology/toxicology team within a review division recommends be a basis for imposition of a clinical hold (full or partial) on an IND.

- The permanent members of the GTRC will include the three OND Office of Drug Evaluation pharmacology/toxicology associate directors (ODE pharm/tox ADs) and the OND associate director (OND AD) for pharmacology/toxicology. The OND AD for pharmacology/toxicology, or his or her designee, will chair the GTRC. In addition to the permanent members, the pharmacology/toxicology reviewers and supervisors from the OND review divisions to which the genetic toxicology studies were submitted will serve as members of the GTRC for the INDs under review. The OND AD for pharmacology/toxicology may also appoint other OND pharmacology/toxicology reviewers to serve as ad hoc members of the GTRC.

- The GTRC will review and evaluate the genetic toxicology study results in cases where the pharmacology/toxicology team in the review division recommends that the studies serve as the basis for imposition of a clinical hold (full or partial). The GTRC will also review and evaluate the pharmacology/toxicology review team's recommendations for additional studies to further evaluate positive findings in genetic toxicology studies.

- The GTRC will provide an interpretation of the studies to the review division director along with advice regarding the biologic significance of any positive findings, as well as recommendations for any additional testing that may be of value in further evaluating positive findings.

- The decision regarding the overall risk-benefit assessment of the drug and the proposed clinical studies remains the responsibility of the review division director; however, the review division director will carefully consider advice from the GTRC and discuss any significant disagreements with the GTRC's recommendations with the chair of the GTRC prior to making a final regulatory decision. If the chair of the GTRC believes that the review division director's regulatory decision is inconsistent with established center policy, the issue will be discussed with the appropriate ODE director for resolution.

- Establishment of the GTRC does not eliminate the need for the genetic toxicology subcommittee of the Pharmacology/Toxicology Coordinating Committee (PTCC). That subcommittee will continue to function as a resource to assist and train pharmacology/toxicology reviewers in assessing the conduct and interpretation of genetic toxicology studies. The genetic toxicology subcommittee of the PTCC will also be responsible for systematically assessing the review of genetic toxicology studies within OND on a periodic basis and hosting appropriate scientific discussions and educational meetings to ensure consistency of the review of genetic toxicology study results within OND.

RESPONSIBILITIES

- It is the responsibility of pharmacology/toxicology team leaders and/or supervisors in the OND review divisions to notify the appropriate ODE pharm/tox AD that a recommendation for imposition of a clinical hold (full or partial) is planned based on the findings in a genetic toxicology study or studies. If the designated ODE pharm/tox AD is not available, the team leader/supervisor should notify one of the other ODE pharm/tox ADs or the OND AD for pharmacology/toxicology. Once the division pharmacology/toxicology review team has determined that genetic toxicology study results serve as the basis for a recommendation for the imposition of a clinical hold, the team leader/supervisor will provide a complete copy of all relevant positive genetic toxicology studies along with the division's preliminary review of the data to all members of the GTRC. This should be done as soon as possible (generally within one to two business days) so as not to impede completion of the review of the IND within the 30-day safety review period. The GTRC should also be provided with the division's preliminary recommendations for additional studies or analyses to further evaluate the positive findings. Because of the time constraints associated with the tertiary review, the committee deliberations may be conducted by e-mail.

- The GTRC will evaluate the positive study results and report its interpretation and recommendations to the review division as soon as possible taking into consideration the 30-day safety review data if applicable. At least one member of the GTRC will

also be available to meet with the review division, if requested, to discuss the GTRC's recommendations. A summary of the deliberations and recommendations of the GTRC will be prepared by the OND AD for pharmacology/toxicology, or a designee, and entered into the Division Files System (DFS). The summary of the GTRC recommendations will be sent to the appropriate pharmacology/toxicology team leader(s), the division pharmacology/toxicology review team members, and the division director(s).

PROCEDURES

- Divisional pharmacology/toxicology team leaders or supervisors will notify the appropriate ODE pharm/tox AD as soon as possible (generally within one business day) of plans to recommend a clinical hold (full or partial) based on genetic toxicology findings. The pharmacology/toxicology team leader or supervisor will provide a copy of all relevant positive genotoxicity study reports, reviews, and other relevant data to the GTRC for review as soon as possible (generally within one to two business days).

- The GTRC will evaluate the data and provide a response to the review division within two working days after receipt of the data. The GTRC tertiary review will include an interpretation of the studies, advice regarding the biologic significance of any positive findings, and recommendations for any additional testing that may be of value in further evaluating positive findings. The GTRC's review and recommendations will be archived in the DFS with a copy to the pharmacology/toxicology reviewer(s), the divisional pharmacology/toxicology supervisor(s) or team leader(s), the IND review team including the regulatory project manager, the medical reviewer(s), the medical team leader(s), and division director(s). At least one member of the GTRC will be available to meet with the division review team to explain the committee's recommendations and to provide any additional assistance necessary to help the review division director in making the final regulatory decision for the IND.

EFFECTIVE DATE

This MAPP is effective upon date of publication.