POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

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

Table of Contents

PURPOSE

- This MAPP establishes policies and procedures in the Office of New Drugs (OND) for tertiary review of data from genetic toxicology studies. This MAPP also establishes a Genetic Toxicology Review Committee (GTRC) within OND to perform the tertiary review.

BACKGROUND

- The ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* specifies the genetic toxicology assays that should be performed and submitted in support of investigational new drug applications (INDs) and new drug applications.[1] Generally, a bacterial gene mutation assay (Ames test) is considered sufficient to support all single dose clinical development trials. To support multiple dose clinical development trials, an additional assessment capable of detecting

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

chromosomal damage in a mammalian system(s) should be completed.[2] 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 therefore could pose a possible carcinogenic hazard. In many cases a positive result in a genetic toxicology test may lead to a decision by a review division director to impose a clinical hold (full or partial) on the IND (particularly with regard to repeat-dose clinical trials) and/or request additional studies to further explore the positive finding before additional clinical trials 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. Other increases in genotoxicity endpoints may be considered artifactual (i.e., false positives) and can occur through excessive toxicity or extremes in culture conditions related to pH and osmolarity.

POLICY

- Tertiary review will occur when positive genetic toxicology study results serve as the basis for imposing a full or partial clinical hold on an IND and/or requesting that additional studies be performed to further evaluate the positive findings.

- Given the potential serious effect of a positive genetic toxicology test on the continuation of a drug development program and the potential safety implications of administering the drug to humans, OND will ensure that these studies are consistently reviewed and interpreted across all OND review divisions. This approach will ensure that review division directors are provided with consistent, high-quality information on which to base their decisions about allowing the proposed clinical trials to proceed. It also will ensure that clinical hold recommendations and requests for follow-up studies will be informed by the best available science and will be consistent across OND review divisions.

- The review division director remains responsible for decisions regarding the overall risk-benefit assessment of a drug and the proposed clinical trials, including the imposition of clinical holds and requests for follow-up studies based on

[2] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.

positive genetic toxicology results. However, the review division director will consider advice from the GTRC when making these decisions.

- The GTRC will not replace the Genetic Toxicology Subcommittee of the Pharmacology/Toxicology Coordinating Committee (PTCC), which will continue to function as a resource to assist and train pharmacology/toxicology reviewers in assessing the conduct and interpretation of genetic toxicology studies. See MAPP 7400.1 Rev. 2 *Management of the CDER Pharmacology/Toxicology Coordinating Committee and Its Associated Subcommittees and Working Groups* for PTCC subcommittee responsibilities.

RESPONSIBILITIES AND PROCEDURES

- The pharmacology/toxicology team leaders and/or pharmacology/toxicology supervisors in the OND review divisions will notify the appropriate office of drug evaluation pharmacology/toxicology associate director (ODE pharm/tox AD) (generally within 1 business day) that a clinical hold (full or partial) and/or follow-up testing is recommended based on the findings in a genetic toxicology study or studies. If the designated ODE pharm/tox AD is not available, the pharmacology/toxicology team leader/supervisor should notify one of the other ODE pharm/tox ADs or the OND Immediate Office Associate Director (OND AD) for pharmacology/toxicology.

- The pharmacology/toxicology reviewer or team leader/supervisor will provide all members of the GTRC with a copy of all relevant genetic toxicology data, the division's preliminary pharmacology/toxicology review of the data, and the division's preliminary recommendations for additional studies or analyses to further evaluate the positive genetic toxicology findings. This information will be provided, generally by email, as soon as possible (generally within 1 to 2 business days) so as not to impede completion of the IND review within the 30-day safety review period when applicable (see MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*).

- The GTRC will review and evaluate the positive study results and report its interpretation and recommendations, generally by email, to the review division pharmacology/toxicology reviewer, team leader/supervisor, and division director within 2 business days, taking into consideration the 30-day safety review date if applicable. The GTRC tertiary review should include an interpretation of the studies, advice about the biologic significance of any positive findings, and recommendations for any additional testing that may further inform evaluation of the positive findings.

- 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 needed to help the review division director in making the final regulatory decision for the IND.

- The pharmacology/toxicology reviewer should briefly summarize the GTRC conclusions in his or her review of the submission.

ORGANIZATION OF THE GTRC

- **Chair** — The OND AD, or his or her designee, will chair the GTRC.

- **Permanent members** — Permanent members include the OND ODE pharm/tox ADs and the OND AD for pharmacology/toxicology.

- **Other members** — In addition to the permanent members, the pharmacology/toxicology reviewers and pharmacology/toxicology supervisors from the OND review divisions to which the genetic toxicology studies were submitted will serve as members of the GTRC for the studies 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.

REFERENCES[3]

1. ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*

2. ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*

3. MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*

4. MAPP 7400.1 Rev. 2 *Management of the CDER Pharmacology/Toxicology Coordinating Committee and Its Associated Subcommittees and Working Groups*

[3] Guidance for industry can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. MAPPs can be found on the Manual of Policies and Procedures Web page at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/27/04	N/A	N/A
2/25/15	Rev. 1	This revision takes into consideration experience of the GTRC after September 2004. The references were updated. The Background section was revised to reflect updates to genotoxicity testing as discussed in ICH S2(R1). The policy, responsibilities, and procedures were updated to reflect that communication occurs between the GTRC and the division pharmacology/toxicology supervisor and reviewer, rather than between the GTRC and the division director. Wording was updated to reflect that communication occurs mainly by email. Reference to the Division Filing System was removed. Reference to the Genotoxicity Subcommittee of the PTCC was revised and reference to MAPP 7400.1 Rev.2 was added.