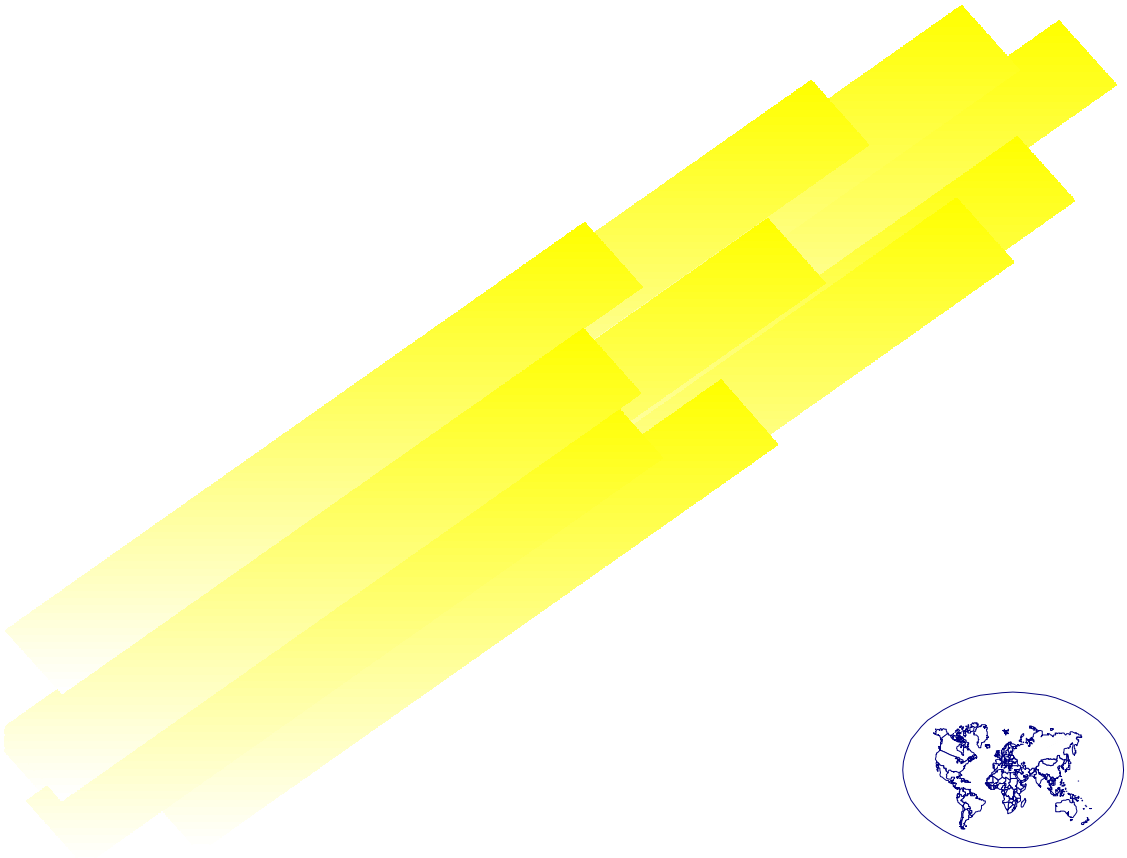
Guidance for Industry

S1C(R) Addendum to *Dose Selection for Carcinogenicity Studies of Pharmaceuticals:* Addition of a Limit Dose and Related Notes



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LIMIT DOSE

In determining the high dose for carcinogenicity studies using the approaches outlined in this guidance, it may not be necessary to exceed a dose of 1500 milligrams (mg)/kilograms (kg)/day (Note 1). This limit dose applies only in cases where there is no evidence of genotoxicity and where the maximum recommended human dose does not exceed 500 mg/day (Note 2).

Data should be provided comparing exposure of rodents and humans to drug and metabolites primarily to support dose selection for and interpretation of the carcinogenicity study. Based on such information, there may be cases where the limit of 1500 mg/kg/day is not acceptable because it cannot be assured that animal exposure after 1500 mg/kg/day is sufficiently high compared to the exposure achieved in humans. The rodent systemic exposure at 1500 mg/kg/day should be greater by at least an order of magnitude than human exposure measured at the intended human therapeutic dose. [If this is not the case, efforts should be made to increase the rodent exposure or to reconsider the animal model in a case-by-case approach.] If the human dose exceeds 500 mg/day, the high dose may be increased up to the maximum feasible dose.

Note 1
Review of the FDA carcinogenicity database of nearly 900 carcinogenicity tests indicated that about 20 tests had been conducted that used doses of 1000 mg/kg or greater as the highest dose tested. About 10 of these tests were considered as having demonstrated a carcinogenic response. Seven of these were positive only at or above 1000 mg/kg, including two that were positive in two species (in neither case were doses above 1000 mg/kg necessary to detect the carcinogenic response in both species, but rather in only one of the two species was a dose greater than 1000 mg/kg necessary).

Some of the one species positives were also only positive at doses greater than 1000 mg/kg. In one case where the drug was considered as demonstrating a significant tumor response only above

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[1]This guidance was developed within the Expert Working Group (Safety) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, July 1997. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States. This guidance was published in the *Federal Register* on December 4, 1997 (62 FR 64259), and is applicable to drug and biological products. This guidance represents the Agency's current thinking on dose selection for carcinogenicity studies of pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

1000 mg/kg, it was positive in several nonstandard genotoxicity assays but not in standard genotoxicity studies. Regulatory action has resulted from some of these cases. Based on these results, the limit dose for carcinogenicity testing should be 1500 mg/kg rather than 1000 mg/kg to eliminate the risk that a genotoxic carcinogen will not be able to be identified as a result of adoption of a limit dose of 1000 mg/kg.

Note 2

It has been agreed that if a nongenotoxic drug is only positive in rodents at doses above those producing a 25-fold exposure over humans, such finding would not be considered likely to pose a relevant risk to humans.

It has been shown that systemic exposure comparisons between rodents and humans are better estimated by dose using mg/square meters (m^2) than using mg/kg (Note 4 of the S1C document "Dose Selection for Carcinogenicity Studies of Pharmaceuticals"). Therefore, the human dose should be at least 25-fold lower on a mg/m^2 basis than the high dose in the carcinogenicity study. The factor, 6-7 (6.5), is used to convert rat doses from mg/kg to mg/m^2 and 40 is used to convert human doses from mg/kg to mg/m^2.

Thus, the estimated systemic exposure ratio of 25-fold rodent to human is equal to about a 25-fold mg/m^2 ratio or a 150-fold mg/kg ratio ($150 \approx 25 \times 40/6.5$). Therefore, a human dose below 10 mg/kg/day (about 500 mg/day or less) could be tested in rats at 1500 mg/kg as the high dose.