concentrations in animals and humans for the assessment of carcinogenic risk to humans. However, for the present, and based on an analysis of a data base of carcinogenicity studies performed at the MTD, the selection of a high dose for carcinogenicity studies which represents a 25 fold ratio of rodent to human plasma AUC of parent compound and/or metabolites is considered pragmatic (NOTE 4).

Criteria for Comparisons of AUC in Animals and Humans for Use in High Dose Selection

The following criteria are especially applicable for use of a pharmacokineticallydefined exposure for high dose selection.

1. Rodent pharmacokinetic data are derived from the strains used for the carcinogenicity studies using the route of compound administration and dose ranges planned for the carcinogenicity study (NOTES 5, 6, and 7).

2. Pharmacokinetic data are derived from studies of sufficient duration to take into account potential time-dependent changes in pharmacokinetic parameters which may occur during the dose ranging studies.

3. Documentation is provided on the similarity of metabolism between rodents and humans (NOTE 8).

4. In assessing exposure, scientific judgment is used to determine whether the AUC comparison is based on data for the parent, parent and metabolite(s), or metabolite(s). The justification for this decision is provided.

5. Interspecies differences in protein binding are taken into consideration when estimating relative exposure (NOTE 9).

6. Human pharmacokinetic data are derived from studies encompassing the maximum recommended human daily dose (NOTE 10).

Saturation of Absorption in High Dose Selection

High dose selection based on saturation of absorption measured by systemic availability of drug-related substances is acceptable. The mid and low doses selected for the carcinogenicity study should take into account saturation of metabolic and elimination pathways.

Pharmacodynamic Endpoints in High Dose Selection

The utility and safety of many pharmaceuticals depend on their pharmacodynamic receptor selectivity. Pharmacodynamic endpoints for high dose selection will be highly compound-specific and are considered for individual study designs based on scientific merits. The high dose selected should produce a pharmacodynamic response in dosed animals of such magnitude as would preclude further dose escalation. However, the dose should not produce disturbances of physiology or homeostasis which would compromise the validity of the study. Examples include hypotension and inhibition of blood clotting (because of the risk of spontaneous bleeding).

Maximum Feasible Dose

Currently, the maximum feasible dose by dietary administration is considered 5 percent of diet. International regulatory authorities are reevaluating this standard. It is believed that the use of pharmacokinetic endpoints (AUC ratio) for dose selection of low toxicity pharmaceuticals, discussed in this guideline, should significantly decrease the need to select high doses based on feasibility criteria.

When routes other than dietary administration are appropriate, the high dose will be limited based on considerations including practicality and local tolerance.

Additional Endpoints in High Dose Selection

It is recognized that there may be merit in the use of alternative endpoints not specifically defined in this guidance on high dose selection for rodent carcinogenicity studies. Use of these additional endpoints in individual study designs must be based on scientific rationale. Such designs are evaluated based on their individual merits (NOTE 11).

Selection of Middle and Low Doses in Carcinogenicity Studies

Regardless of the method used for the selection of the high dose, the selection of the mid and low doses for the carcinogenicity study should provide information to aid in assessing the relevance of study findings to humans. The doses should be selected following integration of rodent and human pharmacokinetic, pharmacodynamic, and toxicity data. The rationale for the selection of these doses should be provided. While not all encompassing, the following points should be considered in selection of the middle and low doses for rodent carcinogenicity studies:

1. Linearity of pharmacokinetics and saturation of metabolic pathways.

- 2. Human exposure and therapeutic dose.
- 3. Pharmacodynamic response in rodents.

4. Alterations in normal rodent physiology.

5. Mechanistic information and potential for threshold effects.

6. The unpredictability of the progression of toxicity observed in short-term studies.

Summary

This guidance outlines five generally acceptable criteria for selection of the high dose for carcinogenicity studies of therapeutics: Maximum tolerated dose, 25 fold AUC ratio (rodent:human), dose-limiting pharmacodynamic effects, saturation of absorption, and maximum feasible dose. The use of other pharmacodynamicpharmacokinetic- or toxicity-based endpoints in study design is considered based on scientific rationale and individual merits. In all cases, appropriate dose ranging studies need to be conducted. All relevant information should be considered for dose and species/strain selection for the carcinogenicity study. This information should include knowledge of human use, exposure patterns, and metabolism. The availability of multiple acceptable criteria for dose selection will provide greater flexibility in optimizing the design of carcinogenicity studies for therapeutic agents. NOTE 1

The following are considered equivalent definitions of the toxicity based endpoint describing the maximum tolerated dose: The U.S. Interagency Staff Group on Carcinogens has defined the MTD as follows:

The highest dose currently recommended is that which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity without significantly altering the animal's normal lifespan due to effects other than carcinogenicity. This dose, sometimes called the maximum tolerated dose (MTD), is determined in a subchronic study (usually 90 days duration) primarily on the basis of mortality, toxicity and pathology criteria. The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study. Nor should it comprise so large a fraction of the animal's diet that the nutritional composition of the diet is altered, leading to nutritional imbalance.

"The MTD was initially based on a weight gain decrement observed in the subchronic study; i.e., the highest dose that caused no more than a 10% weight gain decrement. More recent studies and the evaluation of many more bioassays indicate refinement of MTD selection on the basis of a broader range of biological information. Alterations in body and organ weight and clinically significant changes in hematologic, urinary, and clinical chemistry measurements can be useful in conjunction with the usually more definitive toxic, pathologic, or histopathologic endpoints." (Environmental Health Perspectives, Vol. 67, pp. 201–281, 1986.)

The Ministry of Health and Welfare in Japan prescribes the following:

"The dose in the preliminary carcinogenicity study that inhibits body weight gain by less than 10% in comparison with the control and causes neither death due to toxic effects nor remarkable changes in the general signs and laboratory examination findings of the animals is the highest dose to be used in the full-scale carcinogenicity study." (Toxicity test guideline for pharmaceuticals. Chapter 5, p. 127, 1985.)

The Committee on Proprietary Medicinal Products of the European Community prescribes the following:

"The top dose should produce a minimum toxic effect, for example a 10% weight loss or failure of growth, or minimal target organ toxicity. Target organ toxicity will be demonstrated by failure of physiological functions and ultimately by pathological changes." (Rules Governing Medicinal Products in the European Community, Vol. III, 1987.)

NOTE 2

While it is recognized that standard test batteries may not examine all potential genotoxic mechanisms, for the purposes of this guideline, a pharmaceutical is considered nongenotoxic with respect to the use of pharmacokinetic endpoints for dose selection, if it is negative in the standard battery of assays required for pharmaceutical registration.

NOTE 3

This does not imply that all possible rodent strains will be surveyed for metabolic profile. But rather, that standard strains used in carcinogenicity studies will be examined.