(a) Reports from Poison Control Centers,

(b) Reports of adverse reactions relative to the product that have been submitted to the company by physicians, hospitals, consumers, and other sources,

(c) Extensive searches of the medical, pharmacological, and toxicological literature, and

(d) For drugs, where the human experience data submitted is based on data required by FDA to be compiled for an Investigational Exemption for a New Drug (IND), 21 CFR part 312, or a New Drug Application (NDA), 21 CFR part 314, a summary of the relevant data should be provided. The entire NDA and IND material need not be submitted.

§ 1702.9 Relevant experimental data.

Experimental data are generated in both animals and humans in controlled situations in order to evaluate the biological effects of a substance. Certain toxicological effects cannot generally be evaluated in human beings. This is especially true of those substances which are not normally intended to be used in or on the human body or animal body. Therefore, the Commission considers experimental data obtained in animal studies to be an important supplement to such data as may exist from any experimental studies conducted in humans. The minimum toxicological evaluation necessary for a particular household substance is proportional to the expected exposure of man to that substance. Household substances which are not expected, in normal use, to contact man are subject to less extensive studies than those substances, such as drugs, which are designed to be used in or on man. The Commission has, therefore, separated the requirements of this section into three subsections. Section 1702.9(a) lists minimum acute animal toxicity data which shall be submitted, if reasonably available, for all petitions; §1702.9(b) lists those additional data which shall be submitted, if reasonably available, for drug products and all other household substances which are normally intended to be used in or on the human body; and §1702.9(c) lists those additional data which shall be submitted, if reasonably available, by petitioners requesting exemption for substances not intended for use in or on the human or animal body. The Commission emphasizes that, while not absolutely necessary, the types of data outlined in §1702.9(c) may greatly expedite the Commission's evaluation of a particular exemption request.

(a) *General criteria applicable to all petitions.* (1) Each petition for an exemption under this part shall include all reasonably available relevant experimental data relating to the petition regardless of whether such data are unfavorable to the petitioner's request. As used in this part, the term "relevant experimental data" includes, but is not limited to, all data, including animal and human studies revealing the nature and degree of the hazard associated with the particular substance. Generally, the hazard associated with the particular substance involves the risk of injury arising from the acute accidental ingestion of a product. Where a hazard different from the risk of injury arising from accidental ingestion is known to exist (e.g., potential for significant allergenicity, dermal or opthalmic injury from handling or using the product), the petitioner shall also submit all reasonably available relevant experimental data evaluating the nature and degree of any additional hazard(s).

(2) All animal studies submitted in support of exemption requests should be performed in conformity with good pharmacological and toxicological practice which includes, as a minimum, complete descriptions of protocols used in experimental animal studies, and signed laboratory reports which include the following basic information:

(i) An exact description of materials tested;

(ii) A description of test animals employed in studies, including number, age, weight, sex and nutritional state of animals;

(iii) Dosage level(s) and number of animals tested per dosage level;

(iv) Basis upon which dosage was administered (e.g., as salt or base);

(v) Route of administration and dosage volume; and

(vi) Appendices containing all raw data and any additional data generated subsequent to the completion of the original study (e.g., results of histopathological examinations, if performed).

(3) Each petition shall include all reasonably available reports of Median Lethal Dosage (LD50) studies and shall include all raw data obtained in such studies. These studies should normally be conducted in both adult and weanling animals of the same species. The oral route of administration should be followed for studies involving substances subject to regulations promulgated under the Poison Prevention Packaging Act of 1970. Where a percutaneous toxicity hazard exists, the petition shall include reasonably available studies using the percutaneous route of administration. Sufficient dosage levels as well as adequate numbers of test animals per dosage level should be used to give statistical reliability to determined LD50 values.

(4) In view of the fact that LD50 values in themselves do not necessarily reflect a true estimate of the overall toxic potential of a substance, LD50 determinations should, where an LD50 value may be calculated, include:

(i) The LD50 value with 95 percent confidence limits;

(ii) A slope determination for the dose response curve, including 95 percent confidence limits; and

(iii) A description of the statistical method employed in the analysis of such data (with proper citation) as well as the statistical analysis itself.

(5) The Commission shall disregard any data which do not fulfill the strict requirements of the statistical method used in their analyses. Modifications of accepted statistical methods which have been published in the literature are acceptable to the Commission provided that a copy of the published work is submitted.

(6) Acute toxicity studies submitted with petitions should have at least a seven day observation period of test animals. Good pharmacological practice provides that test animals are observed closely for several hours following test substance administration and less frequently on subsequent test days. Succumbing animals should be necropsied as soon as practicable following death, while surviving animals should be necropsied, and gross pathological alterations noted, at the end of the observation period. Documentation of non-lethal effects occurring during these observation periods should be submitted in conjunction with acute toxicity laboratory reports. Documentation of any lethal effects occurring at high dosage levels, including mode of death (e.g., cardiac arrest/respiratory arrest), and time of death should be submitted in conjunction with acute toxicity laboratory reports. Reports of gross necropsies performed upon surviving animals should be submitted, as well as results of necropsies performed upon animals succumbing to the test substance, provided that such animals are examined prior to the onset of autolysis. Results of microscopic examinations, when indicated by the nature or results of an acute toxicity study, shall also be submitted.

(b) *Additional data criteria for petitions involving substances normally used in or on the human or animal body.* (1) Petitioners submitting exemption requests for substances normally used on or taken into the human body or animal body shall, in addition to the requirements of paragraph (a) of this section submit the following data, where reasonably available:

(i) Summary laboratory reports of data obtained in subacute and chronic animal studies where the data pertain to the absorption, distribution, metabolism and excretion of substances in question;

(ii) A median lethal dosage (LD50) determination conducted in one additional species. Of the two LD50 determinations required for persons submitting exemption requests under this part, one should be conducted in a nonrodent species;

(iii) Summary reports of data obtained in human studies designed to measure the absorption, distribution, metabolism, and excretion of substances in question; and

(iv) Data indicating, insofar as is known, the mechanism of action of the substance in question and the mechanism by which expected toxicological effects occur. If these mechanisms are

unknown, the petition should state this.

(2) Petitioners submitting exemption requests for substances normally used on or taken into the human or animal body shall, in addition to the requirements of paragraphs (a) and (b)(1) of this section, submit an evaluation of the pharmacology and toxicology of the substance in question based on reasonably available medical and scientific literature. The evaluation should be a comprehensive one, and should include proper literature citations. To the extent possible, information submitted by the petitioner justifying an exemption based on the medical and scientific literature will be evaluated under the criteria specified in §1702.9(a) for evaluating experimental data. In certain cases where the experimental data specified by §1702.9 (a) and (b) are unavailable, the medical and scientific literature may justify granting an exemption, particularly where the pharmacology and toxicology of the substance is well documented in the literature.

(c) *Optional data criteria for petitions involving substances not used in or on the human or animal body.* The following types of data, although often not generated for household substances not normally used in or on the human or animal body, may be available to a petitioner and should, where reasonably available, be submitted.

(1) Summary laboratory reports of data obtained in subacute and chronic animal studies where such data pertain to the absorption, distribution, metabolism, and excretion of the substance in question;

(2) Results of median lethal dosage (LD50) studies conducted in additional species of animals; and

(3) Any additional experimental studies relevant to the exemption request which would provide the Commission with additional means of assessing the hazards to children of the product for which exemption is sought.

§ 1702.10 Human experimental data involving the testing of human subjects.

Any human experimental data submitted with a petition requesting an exemption under this part shall include a statement establishing that adequate measures have been taken to ensure against psychological or physical injury to the subject of the human studies. The Commission considers its regulations concerning the protection of human subjects (16 CFR part 1028) to be an example of measures that are adequate to ensure against psychological or physical injury to human subjects.

§ 1702.11 Product specifications.

Each petition for an exemption shall include:

(a) A complete quantitative formula for the product, including inert ingredients, diluents, and solvents. (Petitioners should refer to §1702.6 for information regarding trade secrets.)

(b) A listing of all physical forms or dosage forms (whichever is appropriate) in which the product is available.

§ 1702.12 Packaging specifications.

Each petition for an exemption shall include the following information for each form of the product for which an exemption is sought:

(a) A description of the packaging currently in use including the name of the manufacturer of the package and all specifications for the package,

(b) A complete packaging description including any carton or wrapping in which the product is offered to the consumer,

(c) A description of each size in which the product is offered, including physical form, color and flavoring, and

(d) An empty sample of each type and size of package petitioned for exemption and, in the case of drugs, a designation of those packages intended to be used in dispensing the product to the consumer for household use.

§ 1702.13 Labeling and packaging samples.

Each petition for an exemption under this part shall include a sample of the label and complete packaging for each size in which each form of the product for which an exemption is sought is packaged. This shall include the immediate container labeling, any package inserts, and other carton or wrapping labeling in which the product is offered to the consumer. In the case of drugs,