Target Animal Safety
Overview

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TARGET ANIMAL SAFETY
DEFINITION OF SAFETY

Adequate tests by all methods
reasonably applicable to show that the
drug is safe for use under the conditions
prescribed, recommended, or
suggested in the proposed labeling

FFDCA Section 512(d)(1); CFR Section 514.1(b)(8)(i)

TARGET ANIMAL SAFETY
TECHNICAL SECTION

• Pharmacologic/toxicologic characterization
• Pivotal Target Animal Safety (TAS)
  study(ies)
• All Other Information for TAS
• Freedom of Information Summary for TAS
• Labeling for TAS
TARGET ANIMAL SAFETY

- Margin of Safety study (e.g. 0X, 1X, 3X, 5X at 3X duration)
- Reproductive Safety study
- Animal Class Safety study
- Special cases (specific breeds, injection site irritation)

TARGET ANIMAL SAFETY

- The goals of the target animal safety study/studies are to identify the toxic effects of the drug and establish a margin of safety for the labeled dosage regimen (dose, route, frequency, duration)
- Target animal safety studies are generally conducted in a small number of healthy animals
- An approval may not require multiple types of safety studies
- Safety information is also collected during the effectiveness studies and in review of All Other Information

Guidance for Industry #185

AKA: VICH GL43 – Target Animal Safety for Veterinary Pharmaceutical Products
- supersedes FDA GFI #33 – Target animal Safety Guidelines for New Animal Drugs
- This harmonized guidance provides recommendations regarding TAS evaluation of a pharmaceutical product, including identification of target organs, where possible, and confirmation of margin of safety, using the minimum number of animals appropriate for the studies.
Guidance for Industry #185

- The margin of safety may be documented if the study includes both the recommended dose and overdoses, given for the proposed and longer treatment periods. The selection of dose and overdose levels and durations of treatment should always be justified by the sponsor, taking into account the proposed use of the product and the known pharmacologic and toxicologic properties of the active pharmaceutical ingredient (API).

Guidance for Industry #185

- Unless otherwise justified by the pharmacologic-toxicologic properties of the API and the proposed use of the product, the design of the margin of safety study should include a negative control, the highest recommended dose level (1X), and two multiples of this use dose (in most cases three times (3X) and five times (5X)) for a period of time in excess of the recommended maximum duration of use [frequently 3X duration].

Guidance for Industry #185

- The product to be evaluated should be the product intended to be marketed. If the market formulation is not used, comparative (bridging) studies may be necessary, e.g., the relevance of TAS data for one formulation of the product to another formulation can be demonstrated by the use of bioequivalence or other data between the two formulations.
Guidance for Industry #185

- The age of animals should be considered carefully; if the product is intended for use in young, immature animals, then the animals in the TAS studies should generally be the youngest age for which product approval is sought. Otherwise, healthy young mature animals should be used.

Guidance for Industry #185

- If food affects API bioavailability, animals should be fed or fasted before drug administration to provide the highest likelihood of showing adverse effects.

Guidance for Industry #185

- The most important techniques for avoiding bias in studies are randomization and masking (blinding).
Guidance for Industry #185

• Gross and microscopic examination of tissues of animals in all dose groups is recommended for products containing a new API, due to the small number of animals used and a general lack of other safety information in the target species.

Guidance for Industry #185

• Results should be evaluated and interpreted based on a combination of medical, toxicologic, and statistical principles with consideration of biological significance and plausibility.
• Units should be appropriate for US or converted to standard US units

Guidance for Industry #185

• Margin of safety studies are generally required for new salts or formulations of an API. Exceptions should be justified, for example, on the basis of known toxicology and target animal safety profiles for the API, widespread clinical use of existing products, and/or where the systemic or local exposure (as applicable) of the new product is proven to be equivalent to or less than that of the existing product.
Guidance for Industry #185

• If systemic exposure to the API is negligible, and based on pre-existing knowledge in pharmacology and toxicology there is no safety concern, then the margin of safety study may not be needed.

Target Animal Safety

• You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact CVM.

http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm12344.htm
REGULATIONS

21 CFR 58 – Describes the Good Laboratory Practices (GLPs) for conducting nonclinical laboratory studies
• A nonclinical laboratory study (NCLS) means *in vivo* and *in vitro* experiments in which test articles are studied prospectively in the test systems under laboratory conditions to determine their safety.

GLPs

The following are not NCLS:
– Studies utilizing human subjects
– Clinical studies or field trials in animals
– Basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

21 CFR 58 - GLPs

Provides specific information on:
1. Personnel - identifies the responsibilities of:
   • each individual involved in the study
   • the testing facility management
   • the study director
   • the quality assurance unit
Quality Assurance Unit

- Inspect each NCLS at intervals adequate to assure the integrity of the study and document that
- Determine that no deviations were made from the protocol without proper authorization and documentation
- Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study

21 CFR 58 – GLPs, continued

2. Facilities – describes requirements of animal care facilities; facilities for handling test and control articles, specimen and data storage
3. Equipment – requirements for equipment used in the generation, measurement, or assessment of data – including maintenance and calibration of equipment
4. Testing facilities operation - shall have SOPs in writing for NCLS that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of the study

21 CFR 58 – GLPs, continued

5. Test and control articles – the identity, strength, purity, and composition of the test and control articles shall be determined for each batch and shall be documented
6. Protocol for and conduct of a NCLS – states that each study shall have a written protocol that clearly indicates the objectives and all methods for the conduct of the study and lists the information that should be included in the protocol
21 CFR 58 – GLPs, continued

7. Records and reports –
   • states that the final study report shall be prepared for each NCLS and lists the information that shall be included in the report
   • Requirements for the storage and retrieval of records and data

8. Disqualifications of testing facilities – sets forth grounds for disqualification, hearing requirements, and grounds for reinstatement

OECD GLPs

• Some sponsors conduct TAS studies in foreign countries, according to OECD-GLPs and state that the study was conducted to OECD-GLPs. Sponsors are still required to report to CVM whether or not they are in full compliance with the FDA-GLPs and if not, the nature of the non-compliance and the impact the non-compliance has on the results and interpretation of the study.
• Perfect compliance with the OECD-GLPs may not result in full compliance with the FDA-GLPs because the standards, though similar, are not identical.

Summary

• Target Animal Safety study(ies) establish a margin of safety
• There are many ways to satisfy the TAS technical section – communicate with CVM on your proposal to address TAS
• Guidance documents available for TAS study conduct
Thank You!

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