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~~Proposal for the~~ Establishment of an Expert Working Group to Elaborate the Requirements to Demonstrate Bioequivalence

~~Proposal Paper for~~Concept Paper to be Considered by the VICH Steering Committee

1. Introduction

Consistent with the diversity in physiology that exists between and among veterinary species and because of the unique kinds of formulations and methods of drug administration associated with veterinary pharmaceuticals, there are numerous complex issues that are unique to the regulation of veterinary drugs in comparison to human drugs. Accordingly, the determination of bioequivalence (BE) in domestic animal species can present a host of statistical, logistical, and regulatory challenges that are not well addressed by the BE guidelines that have been elaborated for human drugs.

The evolving therapeutic landscape further complicates the ability to define product BE as it ushers in the use of novel delivery systems, alternative methods of drug administration, and active pharmaceutical ingredients (APIs) that may be difficult to define (e.g., biomass products and large molecules). Therefore, as science moves forward, new challenges face regulators, innovator firms and generic drug sponsors as BE concepts are applied to support the approval of formulation changes or new generic drug applications. Efforts to address these challenges are difficult at best within any particular jurisdiction. Efforts for international harmonization of BE requirements or, at the very least, the kinds of test methods that can be applied to evaluate the BE of these novel therapeutics will be effectively impossible unless we first establish a unified agreement with respect to the basic or fundamental pharmacokinetic, biopharmaceutic, and statistical principles upon which all BE assessments are based. It is with an appreciation of the need for harmonization of these fundamental principles that has led to this proposal to establish an Expert Working Group within VICH to examine the similarities and differences between countries/regions, to come to agreement on, and to elaborate the basic requirements to demonstrate bioequivalence for veterinary drugs.

International differences in addressing these challenges and in defining the criteria for determining BE can lead to barriers in international data exchange, scientific confusion, and the need for drug sponsors to conduct multiple investigations to meet regional registration requirements. Therefore, there is a great need for fostering harmonization efforts. This need to foster an understanding of basic principles has already been addressed within the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), where a general BE guideline has been developed to describe drug bioequivalence requirements in the Global Cooperation Group countries.[1]

Within the context of the current VICH proposal, the first step in harmonization would be to ensure that a universal definition of BE is achieved and that all parties are in agreement with the underlying fundamentals essential to all BE assessments. As part of that goal, a harmonized guideline would address the basic principles, considerations, and BE targets associated with *in vivo* blood level studies used to determine BE. The harmonized guideline would serve as one of the important controls to ensure that all products, regardless of their place of origin, will contribute to the production of a safe, global food supply and to the well-being of all animals.

Once the objective of reaching consensus on the basic principles underlying BE assessments is achieved, additional guidelines might in the future be drafted to address the more unique and complex BE issues associated with veterinary medicines.

2. Problem:

[1] The ICH Global Cooperation Group was formed on March 11, 1999 as a subcommittee of the ICH Steering Committee. Please see (http://www.ich.org/LOB/media/MEDIA4871.pdf).

The current concern is that even for the simplest of situations, the registration requirements for demonstrating BE for animal health products vary widely from region to region. Although Japan, EU, and U.S. have developed (or are developing or revising) BE guidelines for veterinary drugs, there are several differences in the guidance documents used to design data packages to demonstrate BE. The magnitude of discrepancies have been documented in the Summary Report of International Bioequivalence Guidelines, authored by Chantal Lainesse, DVM, Ph.D. (June 4, 2008) (please see the attached report). Furthermore, there are numerous jurisdictions for which it has been difficult to access the most current information in this area. As a result, there is confusion. For example, our current information indicates that there are no veterinary BE guidelines in India and China; Brazil and Argentina both have BE guidance in early development but many other countries in South America do not have veterinary BE guidance; and Canada and Mexico ~~is~~are very close to a final guidance document.

The development of a grass-roots guideline will unify the global veterinary community understanding of the basic pharmacokinetic and statistical principles upon which BE determinations are based. It will also provide a very critical springboard from which we can begin to address some of the complex BE issues that are already beginning to be confronted by regulators as generic applications for novel dosage forms and drugs are being sought by generic drug sponsors.

3. Impact on Public Health, Animal Health, and Animal Welfare:

When dealing with veterinary pharmaceuticals, the two critical public health issues are:

1. Development of drug resistance
2. Human food safety

With regard to resistance development, assurance of comparable rate and extent of exposure is essential for insuring that the safety and effectiveness profile of the pioneer product successfully transfers to the generic alternative. The development of resistance also has a direct impact on animal health and animal welfare, as ineffective drugs are not useful in treatment or prevention regimens. Particularly in a global environment, the development of parasitic or microbial resistance within one jurisdiction can affect the safety and effectiveness of products in surrounding jurisdictions. Therefore, to minimize the risk of a dwindling effective therapeutic arsenal (which will impact both humans and veterinary species), we need to insure that generic alternatives meet the same standards. These standards are born out of years of scientific research and experiences in nations where much of the drug development has taken place. The importance of minimizing the selection of resistant pathogens impacts not only food animals but also companion animals and their human companions.

With respect to human food safety, concerns associated with violative residues and microbial safety (associated with antimicrobials) need to be considered. Microbial safety is established on the basis of insuring equivalent drug bioavailability for the innovator and generic formulations. Furthermore, for reasons that are obvious, assurance of equivalent drug residues within edible tissues is essential for public health, particularly when we consider the importance of international trade in food produced from animals.

4. Anticipated Benefit:

a. Industry: The resulting guidance would serve both as an important teaching tool in non-VICH countries and as a roadmap which will encourage international dialogue based on a common BE framework. Through harmonization and mutual understandings, sponsors can develop one study (or one group of studies) that can be used to cover regulatory requirements for establishing product BE in a global environment.
b. Regulatory authorities: The VICH guidance development process provides a platform for exploring differences in BE criteria, for discussing molecular categories/classes

where harmonization of criteria would be beneficial, for exploring problems that need additional investigation (with the possibility of harmonizing efforts to explore potential solutions and/or conduct *in vivo*, *in vitro* or *in silico* investigations), for providing global consistency in reviewing BE studies, and for ~~and~~ identifying areas where additional guidance/harmonization efforts will be needed in the future.

5. Discussion:

This guideline would differ from other VICH guidelines in that a primary focus would be on scientific principles. Furthermore, such a guideline will provide opportunities for identifying situations when criteria may differ. If so desired, the rationale for these differences can also be provided. Most importantly, the fundamental principles, which unite requirements across jurisdictions, will be carefully laid out, providing the pharmacokinetic and statistical principles to form the basis for sound study designs.

As veterinary medicine and pharmaceutical sciences, in general, move forward, the animal health industry is witnessing a rapid evolution in novel dosage forms, rapid changes in veterinary therapeutics, and a growing need for ensuring international harmonization to accommodate the burgeoning global marketplace. We are seeing new challenges for which global BE criteria cannot even be considered until we have resolved inconsistencies currently facing BE assessments associated with small molecules. With these thoughts in mind, we hope that through this harmonization effort, we will initiate productive steps towards meeting the current and future challenges facing veterinary pharmaceutics.

6. Recommendations:

VICH should establish an Expert Working Group (EWG) to elaborate harmonized guidelines utilizing the basic principles underlying BE determinations. With this in mind, the issues to be addressed are as follows:

1. The definition of BE.
2. Situations where it is appropriate to use blood level BE studies.
3. The factors/variables necessary to consider when developing scientifically sound BE study designs. This section needs to expand upon the scientific and statistical rationale for these approaches and the scientific /statistical criteria that cannot be violated if the design is to remain valid (e.g., half lives to be covered, subject demographics, species selection, reference product selection, dosing conditions, sampling schedules, study power considerations, how to estimate number of subjects needed to achieve the necessary power for any given acceptable ratio of treatment means, replicate study designs, handling outliers, data transformation, etc).
4. Analytical method validation.
5. Jurisdiction differences in criteria.
6. Situations where BE criteria may need to be constrained due to safety and/or efficacy concerns (for example, where resistance may be an issue).
7. Simulated datasets to explore implications of how profiles may differ as C_{max} varies but AUC remains constant to support similarities/differences in criteria across jurisdictions.
8. When residue depletion studies are needed.
9. Complex problems for potential future exploration.
10. Consider where the study report requirements may be standardized.

7. Timetable and Milestones:

VICH Step 2 (total time = 10 months)

1. Form EWG (3 months)
2. EWG (or subgroups of EWG) to cover:
    a. Development of a document covering points 1-4 and 8 – 10 (6 months).

b. The issues delineated in points 5 – 7 (6 months in parallel with subgroup working on point a)

3. Merge documents and complete for internal deliberations (1 month)

VICH Step 3: 3 months

VICH Step 4: 5 months

VICH Step 5: 3 months

VICH Step 6: 4 months

VICH Step 7: 1 month

VICH Step 8: 6 months

VICH Step 9: Depends upon how the EWG decides to address the additional complex questions

8. Impact Assessment:

Industry:

a. Clarity of requirements
b. Reduction in number of studies needed for global marketing
c. Increased global marketing of supplements (e.g., formulation changes) of innovator firms
d. Global consistency in reviewing BE studies

Regulators:

a. Increase in clarity of requirement (less uncertainty expressed by Industry)
b. Decrease in submission of failed studies
c. Lower risk of finding violative residues
d. Global consistency in reviewing BE studies

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