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VICH GL 36: Concept Paper Requesting Revision of the Guideline

Introduction

In the First VICH Conference held in Brussels in 1999, it was concluded that the Safety Working Group (SWG) needed to address the effects of antibiotic residues on the human intestinal flora as part of their mandate. The VICH Steering Committee (SC) approved the formation of a Task Force composed of microbiologists that should study this issue and propose a guideline on this matter to the SWG.

A Task Force was formed in 2000 with government and industry representatives from all VICH regions. The Task Force met four times, between July 2000 and April 2002, until a draft guideline was presented to the SWG in 2002. The Guideline entitled "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI" was finally approved for implementation by the SC as VICH GL 36 in May, 2004.

After four years of working with VICH GL 36, it was evident to USA and EU regulators that sponsors of new antimicrobial drugs could address effects of antimicrobial residues on human intestinal flora in different ways and using different protocols. It was also evident that additional guidance regarding certain methods and assays referred to in GL 36 would be useful.

In view of the above, the FDA-Center for Veterinary Medicine (CVM) decided to call a meeting with scientists that have been working with VICH GL 36, to exchange experiences gained while working with this guideline. A meeting was held on April 28-30, 2008, with 11 international scientists from the EU, Canada, and the USA, and including government and industry representatives, and private consultants. The group reviewed the process of establishing a microbiological ADI applying relevant data, according to VICH GL 36 and agreed that the logic of the systematic approach has been useful in determining whether a microbiological ADI is needed for new antimicrobial drugs. The participants did not exchange any information, data, or decisions regarding any specific drug application but did discuss experiences. During the second day of the meeting, the scientists wrote a document entitled "Experiences Gained Implementing VICH GL 36: Report of an Ad hoc Group of Scientists". This document, which proposed that GL 36 should be strengthened by the addition of more detailed guidance in a number of areas, was sent to the VICH SC, distributed to the regions, and discussed at the July 2008 meeting of the Steering Committee (SC) in Paris. However, AHI supported by IFAH-Europe, argued that opening up GL 36 for review, in line with the report of the meeting convened by the FDA-CVM, might lead to a guideline with limited flexibility, which could generate further problems. While all parties agreed that further scientific discussions are needed in relation to the guideline, there was no consensus within the SC

to re-open the guideline. Following the SC meeting the FDA and EMEA discussed the issue further and concluded that all sides may see an advantage if only that section of the guideline that has been the greatest focus of concern for regulators and industry is opened up for review, with a view to providing additional guidance in this specific area only. In this way the flexibility of the guideline as a whole could be maintained but clarification would be provided over the particular area that has generated most controversy.

The objective of this paper is to briefly specify the sections of VICH GL 36 that are considered by the FDA and EMEA to be most in need of clarification and/or further guidance. The paper also delineates the benefits that a revised guideline would represent for government and industry in relation to the assessment following VICH GL 36.

Problem Statement

It is the consensus of a meeting of representatives of the international community that the systematic approach presented by GL 36 for determining the need for a microbiological ADI for antimicrobial residues (Steps 1-5) has been useful for deriving a microbiological ADI, when needed. However, while going through the steps defined in the guideline, it is evident that questions may arise concerning methods and assays for studies used to answer the question posed in step 3 as well as in the interpretation that can be given to these studies. It was the consensus of the group that the guideline would benefit from more clarification on this issue. The regulatory bodies now have some experience on protocols and testing methods used by industry for obtaining supporting information to address step 3 of the guideline. The experience obtained might result in clarifying certain areas of the protocols and testing methods that would result in a better and more defined study for the purpose of obtaining the desired data.

Impact for Public Health, Animal Health, and Animal Welfare

A better defined and clearer VICH GL 36 would be highly beneficial to public health. Clarifying areas relevant to step 3 of the guideline and suggesting approaches that have been shown to be useful would contribute to improved guidance for sponsors of new antimicrobial drugs.

This guideline does not have any impact on animal health. However, animal welfare would benefit if *in vitro* testing systems were to be found to be as useful as *in vivo* systems for obtaining data necessary to address the guideline.

Anticipated Benefit to Industry, Other Interested Parties, and Regulatory Authorities

Additional guidance relevant to step 3 of the guideline would be highly beneficial to industry as it would facilitate a more focused approach, it would improve the predictability of regulatory decisions and could even translate into shorter review times and consequently, lower expenses for the regulated industry. In addition, improved guidance in this area would also result in a more harmonized review process by

international regulatory bodies leading to similar conclusions concerning the safety of the product. This would benefit industry looking for global approval of their products because it could mean saving of time and money in the generation of data necessary to address the guideline.

For regulatory authorities improved guidance would reduce the overall time necessary for derivation of the most appropriate microbiological ADI for the product. The impact of antimicrobial residues on human intestinal flora could be effectively addressed with fewer meetings between drug sponsors and regulatory officials and the submitted information would be more likely to meet the regulatory agency's needs.

Discussion

The stepwise approach recommended in GL 36 for determining the need for a microbiological ADI has been useful and remains appropriate. However, more guidance and clarity is needed regarding the data necessary to address step 3, which states "*Do the residues entering the colon remain microbiologically active*?" Different interpretations of the data requirements have led to disagreements between regulators and industry with a consequent impact on the time required for the evaluation of dossiers. In order to help avoid similar disagreements in the future, additional guidance should be provided on the issue discussed below.

Methods for defining the fraction of oral dose available to microorganisms. The recommendation to use ADME data to address Step 2 of the guideline is appropriate. These data allow prediction of an approximate percentage of residues reaching the human intestinal colon. However, clarity would be improved if the guideline addressed the following issues related to the fraction of oral dose available to microorganisms:

Concerning Section 2.4.1.1., *"The fraction may be lowered if the applicant provides quantitative in vitro or in vivo data to show that the drug is inactivated during transit through the intestine;"*specifically, more precise guidance is needed on methods to determine the fraction of oral dose available remaining microbiologically active in the intestine, both for *in vitro* and *in vitro* testing methods. Recommendations would be useful for specific test systems (e.g., fecal slurries) and analytical methods (disk diffusion, microbiological cylinder plate assay, changes in bacterial populations, chemical methods, etc.) to determine bacterial exposure to active bound and non-bound drug. Some specific methodological aspects include the following:

a) Dose levels and fecal concentrations to be tested in *in vivo* and *in vitro* testing systems.
b) Source and number of fecal samples.
c) Selection of dose levels and range of doses to be tested. Should they be based on therapeutic levels, residue levels, or both?
d) Appropriate incubation period of feces in the presence of drug.
e) Methods to quantitatively detect microbiologically active drug.
f) Impact of sterilization on the determination of the fraction of dose available to bacteria.

g) Considerations in the selection of indicator bacteria for determining bioavailable drug.
h) Test systems that could be appropriate for determining fraction of fecal slurries that bind to drug.
i) Possibly application or modification of current sorption/desorption studies used in environmental sciences to address bioavailability of drugs in the human intestine.
j) Clarification of appropriate controls to be used in the studies.
k) Guidance on statistical considerations in the design of the study.
l) Diluent components (e.g., minerals, bile acids) that should be considered while processing and diluting fecal material (e.g., pH, atmospheric and redox conditions).
m) Guidance on appropriate parameters (e.g., repeatability, assay ruggedness) that are needed for assay validation.

Finally, the provision of guidance on the appropriate interpretation of data aimed at defining the fraction of an oral dose available to microorganisms would represent a valuable step towards ensuring a harmonized understanding of the relevant part of the guideline.

Recommendation

The FDA and EMEA technical experts recommend that the VICH SC accept this abbreviated concept paper discussing the rationale for revising areas of GL 36 relevant to the establishment of the fraction of the oral dose available to microorganisms. After discussion of this abbreviated concept paper, the above parties recommend that the VICH SC recall the Task Force of experts to develop additional guidance in this area. The guideline has been implemented for over four years and FDA and EMEA experts believe that the experience gained by the regulatory bodies and industry while working with a number of antimicrobial agents will result in fructiferous discussions and a more clear and defined guideline.

Milestones

December 2008: concept paper submitted to the VICH SC.
December and January, 2009: request and compilations of comments from the regions
February 2009: decision by the SC concerning the proposed revision of GL 36 as requested by FDA and EMEA experts.