Microbiological ADI Expert Working Group

Chairperson: A. Haydée Fernández (US FDA)

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Introduction

The use of antimicrobial agents in food producing animals may result in low concentrations of drugs or their metabolites in food of animal origin. Therefore, risk assessment procedures by regulatory authorities determine if acceptable daily intakes (ADIs) of these veterinary drug residues are needed. From a microbiological safety perspective, the ingestion of residues of antimicrobial agents in food of animal origin has the potential hazard to alter the ecology of the intestinal flora if present in sufficient amounts.

EWG Composition

A. Haydée Fernández – Chair (US FDA, g); Silvia A. Piñeiro* (US FDA, g); Takashi Aoki (JMAFF, g); Tetsuo Asai (JMAFF, g); Carl Cerniglia (US FDA, g); Christian Friis* (EU, g); Warren Hughes* (AU/NZ, g); Susan Kotarski (AHI, i); Xian-Zhi Li (Canada, g); Hiroaki Matsumura* , Mitsuaki Sakashita (JVPA, i); Christine Schwarz (EU, g); Tom Shryock (AHI, i); Peter Silley (IFAH-Europe, i); Shabbir Simjee (IFAH-Europe); and S. Steve Yan (US FDA, g)

***** Indicates those who are not in the photo but will participate in current/future work

Government (g), Industry (i)

Development of GL 36

In 2004, VICH adopted VICH GL-36 which provided a general approach to establish a microbiological ADI to evaluate the safety of residues of veterinary drugs in foods of animal origin.

After a few years of working with VICH GL-36, it was evident to regulators that sponsors of new antimicrobial drugs could address effects of antimicrobial residues on human intestinal flora in different ways and using different methods or protocols. Therefore, the US FDA Center for Veterinary Medicine (CVM) called a meeting to exchange experiences gained by scientists working with this guideline. The meeting, held on April 2008, included 11 scientists from government, industry, and private consultants from the EU, Canada, and the USA. The group concluded that the systematic approach presented in GL-36 to determine whether a microbiological ADI is needed for new antimicrobial drugs has been useful, but more clarity was needed in some sections. As recommended by the VICH Steering Committee following their 2008 fall meeting, the FDA and EMEA concluded that a revision of the guideline should focus on the specific section that was the most controversial, i.e., "fraction of oral dose available to microorganisms" (Section 2.4.1.1.).

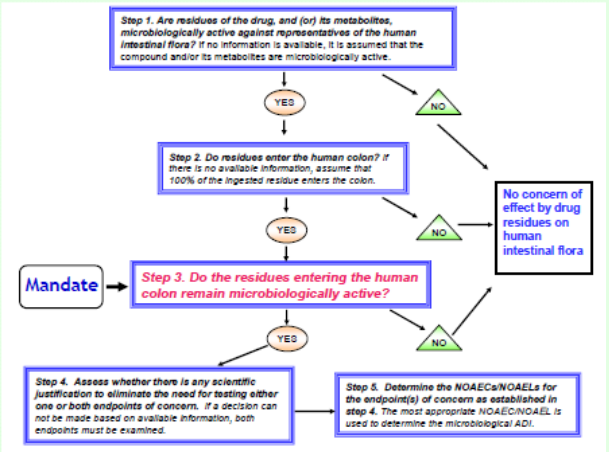
Chronology of GL-36 Developments and its Current Status

Year	Event	Action and activities
1999	I VICH Conference (Brussels)	Mandate to the EWG to consider effects of residues on intestinal flora
2000	Microbial Safety Task Force formed	Multiple meetings held to draft the GL
2002	Draft GL presented to SEWG	EWG accepted draft with modifications
2004	GL-36 presented to Steering Committee	Implementation recommended
2008	US FDA-CVM called a meeting of scientists to discuss GL-36 and prepare a concept paper	a) scientists recommended areas that could be more clearly defined; b) recommendation to provide more detail in the guideline
2009	SC approved revision of GL-36	Established GL-36; EWG to detail approaches to Step-3 of the VICH process
2010	Revision of GL-36: work ongoing by the SEWG through electronic discussion	Focus on "fraction of oral dose available to microorganisms".

Key scientific issues

The guideline offers a step-by-step approach to determine if antimicrobial drug residues reaching the colon remain microbiologically active, and whether a microbiological ADI determination would be necessary (see the diagram below).

The guideline defines the endpoints of public health concern as:
(a) Disruption of the colonization resistance barrier, and
(b) Increase in the population(s) of resistant bacteria in the human colon.



Update of Activities

The group is currently focusing on Step 3, "Do the residue entering the colon remain microbiologically active?". More precise guidance is needed on *in vitro* and *in vivo* testing methods to determine the fraction of oral dose available remaining microbiologically active in the intestine. 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.