VICH Task Force for Efficacy Studies for Combination Products

Progress Report for the 31th SC / 5th VOF meeting in Washington D.C.

Charges

The task force (TF) was charged to elaborate a discussion paper describing a more focused scope for the development of a VICH guideline (GL) for efficacy studies for the combination of veterinary drugs, after the concept paper submitted by Chinese delegation[1] through VICH Outreach Forum (VOF) initiative.

The TF will prioritize the target products for the (one or several) GL(s). The TF will also explore the possibility of creating a general policy document for combination products.

Membership

Total of 12 organizations from the VICH/VOF countries/regions have been registered in the TF where a member from Argentina also represent CAMEVET, and 11 persons nominated as follows.

VICH members	JMAFF (chair)	K. Noda
	JVPA	E. Oishi
	IFAH-EU	M. Bobey
	EU	K. Healey
	US FDA	C. Groesbeck
	AHI	B. McKusick
Observer	South Africa, National Dept. health	V. Naidoo
VOF members	China PR, IVDC	S. Xu
	Argentina, SENASA / CAMEVET	L. Sbordi
	Taiwan, Council of Agriculture	T-R. Jan
	UEMOA	K.Th. Domagni

Actions

As a first step, the TF will develop a catalogue of main groups/classes of approved combination products in VICH and VOF countries/regions in order to ensure a proper knowledge of the existing situation and to perform an efficient needs assessment before developing a VICH GL.

After finishing the first task we will further develop a catalogue of relevant guidance/guidelines for combination products already in place in VICH members and analyse them in terms of structure and elements included.

[1] Concept paper on the Needs to Develop a VICH Guidance for Efficacy Studies for Combination Drug Products (Draft) (VICH/IN/13025)

Survey results and discussion

Part 1: Combination products approved in VICH and VOF countries/regions

Table 1 shows the summary math of the answers to the questionnaire circulated to collect data on the main/major veterinary combinations in a country/region, so far submitted from the TF members. Antiparasitics (AP) combination received total of 27 voting followed by 12 of antimicrobials (AM) combination.

During the electronic discussion of the TF, EU member insisted not to include AM combination as a target category for the putative product type specific GL. In addition, at the 30th SC meeting in Brussels, June 2014, the EU delegate indicated that they would not support the development of a specific GL for combination products consisting of antimicrobials as regulators do not wish to encourage new developments of the AM combination except in very particular circumstances (e.g., sulphonamides and trimethoprim) and a VICH GL on such combination products could be misunderstood as encouragement to non-VICH/VOF countries for their development. It was considered useful to convey such thinking in a general guidance.

There is already a broad consensus within the TF as well as SC members regarding the needs for the development of a general GL, which should include general considerations for combination products, and the GL for addressing AP combinations, based on the analysis of such guideline/guidance already in place in VICH region (Part 2 of this report).

Typical ingredient of the major combination product is listed in Table2. Majority of these products are approved for treatment and prophylactic use for food producing and/or companion animals; only a few are for metaphylactic or growth promotion use (data not shown). It should be noted antimicrobial agents for growth/ feed efficiency promotion is regulated under feed safety legislation rather than pharmaceutical legislation in Japan, hence it is outside the reach of VICH. The task force should also collect such individual situation for the sake of decision making by the SC.

Part2: Guidance/Guideline for combination product already in place

As summarized in Table 3.1 and 3.2, a total of 6 items were submitted from the TF members and through a personal communication. Item #1 to #3 are from EU, #4 from US/FDA and #6 and 7 from Dr. Peter Holdsworth, the president of World Association for Advancement of Veterinary Parasitology (WAAVP), who pointed out Australia should have been involved in the TF as the AP is a major VMP (50% of whole sales) in Australia who had formally adopted WAAVP GL to its regulation recently.

Item #1 is the EU general GL for combination product, while #2 is additional Q&A document specialized in AP combination (the URL provided is not working) and #3 is legal basis for the GL; therefor #1 thought to be a main analyte for the TF.

Item #4 is the US general GL for combination product that is equivalent to the European GL; we should analyse this item in comparison with #1.

Item #5 was created by a group of academic and industry members of WAAVP specialized in combination anti-parasitic product for horses and ruminants. Although #5 was published in academic journal, it was formally adopted by the Australian government as a part of its VMP regulation. Both WAAVP and APVMA recommend using this GL in conjunction with the

existing GL (WAAVP and VICH) for single-constituent active pharmaceutical ingredients (APIs).

Table 4 shows the structural difference among the guidance/guideline from EU/CVMP (#1), USFDA/CVM (#4) and WAAVP (#5).

The main body of #1 CVMP GL is comprised of “Discussion” and “Dossiers requirement” providing overall view to this kind of product application, while #4 CVM GL has merely “Discussion” lacking “Dossiers requirement” part. The discussion part of the two document consist of similar elements of regarding the interaction or interference of the APIs, rational or advantage for combining, how to assess the product efficacy and safety etc. The major difference between them seems that #1 considers not only efficacy but also safety aspect that is outside the scope of the TF, while #2 is focused on efficacy only. The #2 discussion part has extremely precise description of efficacy evaluation for at the “Combination Claims and Treatment Comparison” section with various exemplifications of combination patterns of active ingredients.

In the “Dossier requirement” part of #1 GL, alongside the efficacy relating requirements, other elements such as toxicity, environmental impact, user and consumer safety issues (residue depletion, withdrawal period) are included.

It is apparent that #1 and #2 are the representative general GLs for the combination product; it would be practical to create an internationally harmonized new GL by extracting appropriate elements from these GLs. In that case, handling of the “safety” relating elements that exist in #1 would be one of the major points of discussion.

The over all structure of #5 WAAVP GL is similar to that of #1 GL, comprised of Discussion and Dossiers requirement part, with a more detailed explanation of current situation and problem statement in the introductory part. The Discussion part is also heavier than #1 and #4 GL for the purpose of providing both “rational” as well as “concerns” for the use of combination products regarding the drug resistance issue. This is because, as pointed out by the EU TF member lately, the use of combination product is sometimes against so called “prudent use” and could be a cause of faster drug resistance development, which was a reason why the EU is moving away from antimicrobial combination products, WAAVP GL is missioned to clarify the advantage of combined product for managing and delaying existing resistance to anthelmintics. Although this GL is intended to provide a scientific basis to the approval of anthelmintic combination products, the intensive thinking of WAAVP for resistance issue might be helpful for the putative creation of the general combination products GL in VICH framework.

In the Dossier requirement part of #5 GL, similar to #1 EU GL, alongside the efficacy relating requirements, safety issue is also included.

One of the main propositions of the #5 GL is the control of drug resistance, which is shared by the current consideration by the TF for the revision of anthelmintic GLs. Both WAAVP and Australian Government recommend to use #5 GL in conjunction with existing VICH and WAAVP GLs for anthelmintic drug of single-constituent active products. The Combination Product TF therefore believes that the inclusion of this #5 WAAVP GL into the VICH framework would reasonably be explored further by the TF for the revision of anthelmintic GLs.

Future work

Based on the progress so far achieved and reflecting a discussion at the 31th SC/5th VOF meeting in Washington DC, the TF will develop a formal discussion paper with full data submitted by the TF members and relevant references.

The TF wishes to include inputs from South Africa and UEMOA to Table 1 and 2, and ideally from Australia/New Zealand as suggested by Dr. Holdsworth, to complete a global catalogue of main groups/classes of approved combination products in VICH/VOF countries/region.

Ken Noda, JMAFF
2 Feb, 2015

Table 1. Major combination-products [Dec 2014]

Combination-category			VICH members						Observer	VOF members				Sub-total	Total
			JMAFF	JVPA	EU	IFAH-EU	US FDA	AHI	S.Africa	ChinaPR	Argentina/CAMEVET	Taiwan	UEMOA		
AP-HI			1		1	1	1	1				1		6	27
AP-Pr			1							1		1		3	
AP-Ec			1		1	1		1			1			5	
AP-EnEc			1	1	1	1		1				1		6	
AP-HI	AP-Pr				1	1								2	
AP-HI	AP-Ec						1			1				2	
AP-HI	AP-x						1				1			2	
AP-EnEc	AP-x										1			1	
AM-Bc			1	1	1	1		1		1	1	1		8	12
AM-Mc														0	
AM-Vr														0	
AM-IM-Bc					1	1				1				3	
AM-Bc	AM-Mc													0	
AM-IM-Bc	AM-Bc										1			1	
AM-Bc	AM-Mc	AI		1	1	1								3	8
AM-Bc	AI				1	1	1	1			1			5	
AM-Bc	AP-Pr			1							1			2	3
AM-Bc	Hormones						1							1	
AI					1	1								2	2
AS														0	0
AS	DI									1				1	1
DI			1											1	1
Vitamins			1											1	1
Vitamins	Minerals		1											1	1
Gastrointestinal			1											1	1
Hormones			1				1							2	2
Cardiology					1	1								2	2
Total / legislation			10	4	10	10	6	5	0	5	7	4	0		61
Total / member status			45						0	16				61	

Table 2.1 Ingredients of combination-products [Dec 2014]

Combination category		JMAFF+JVPA	EU+IFAH-EU	US FDA+AHI	ChinaPR	Argentina/CAMEVET	Taiwan
AP-HI		Ivermectin+pyrantel, Praziquantel+pyrantel+febantel, Emodepside+praziquantel,	Praziquantel+pyrantel+febantel, Pyrantel+febantel, Praziquantel+fenbendazole, Derquantel+abamectin, Moxidectin+triclabendazole, Emodepside+praziquantel,	Ivermectin+clorsulon, MilbemycinOxime+praziquantel, Emodepside+praziquantel, Febantel+praziquantel+pyrantel			Febantel+praziquantel+ pyrantel
AP-Pr		Sulfadimethoxine, pyrimethamine, Glycarbylamide, dinitolmide,			Amprolium+ethopabate, Sulfaquinoxaline,		Amprolium+ethopabate +sulfaquinoxaline,
AP-Ec		Fiproni+amitraz+(s)-methoptrene, Imidacloprid+moxidectin,	Indoxacarb+permethrin, Fipronil+amitraz+(S)-methoprene, Dinotefuran+permethrin+pyriproxyfen, Metaflumizone+amitraz, Imidacloprid+flumethrin, Fipronil+permethrin,	Fipronil+(S)-methoprene, Fipronil+cyphenothrin,		Imidacloprid+permethrin+piperonyl butoxide, Cipermethrin+ethion,	
AP-EnEc		MillbemycinOxime+lufenuron, MilbemycinOxime+spinosad, Ivermectin+pyrantel	Imidacloprid+moxidectin, Spinosad+milbemycin , MilbemycinOxime+Lufenuron, Closantel+mebendazole, Closantel+ivermectin, Praziquantel+ivermectin, Eprinomectin+fipronil+praziquantel+(S)- methoprene,	Ivermectin+praziquantel, Ivermectin+clorsulon, Imidacloprid+Ivermectin, MilbemycinOxime+ lufenuron, MilbemycinOxime+lufenuron+praziq uantel, Imidacloprid+moxidectin,			Ivermectin+pyrantel
AP-HI	AP-Pr		Emodepside+toltrazuril,				
AP-HI	AP-Ec			Emodepside+praziquantel,	Narasin+nicarbazin, Ivermectin+albendazole, Fipronil+methoprene+amitraz,		
AP-HI	AP-x			MilbemycinOxime+lufenuron+Praziq uantel, MilbemycinOxime+lufenuron,		Pyrantel+fenbendazole+praziquantel, Albendazole+praziquantel,	
AP-EnEc	AP-x					Ivermectin+clorsulon, Ivermectin+nitroxinil, Ivermectin+abamectin,	

Table 2.2 Ingredients of combination-products [Dec 2014]

Combination category			Japan	EU	USA	ChinaPR	Argentina	Taiwan
AM-Bc			Benzylpenicillin+dihydrostreptomycin, Benzylpeniciliin+kanamycin, Oxytetracycline+fradiomycin, Benzylpenicillin+streptomycin, Benzylpenicillin+dihydrostereptomycine,	Amoxicillin+clavulanate, Trimethoprim+sulfonamide,	Amoxicillin+clavulanate,	Trimethoprim+sulfonamide, Amoxicillin+clavulanate, Tylosin+sulfamethazine	PenicillinG sodic+penicillinG procaine +PenicillinG benzatine+Streptomycine	Trimethoprim+sulfonamide
AM-IM-Bc				Cefapirin+Prednisolone, Penicillin+framycetin, Cephalexin+kanamycin,		Cloxacillin+ampicillin, Lincomycin+neomycin,		
AM-IM-Bc	AM-Bc						Amoxicilin+cloxacillin, Ampicillin benzathine+cloxacillin benzathine,	
AM-Bc	AM-Mc	AI	Nystatin+thiostrepton+fradiomycin+triamcinolone	Gentamicin+miconazole+hydrocortisone, Orbifloxacin+mometasone+posaconazole, PolymyxineB+miconazole+prednisolone,				
AM-Bc	AI			Florfenicol+flunixin,	Florfenicol+flunixin, Oxytetracycline+flunixin, Enrofloxacin+Silver Sulfadiazine, Gentamicin+Betamethasone,		Tilmicosin+ketoprofeno, Ceftiofur+ketoprofeno,	
AM-Bc	AP-Pr		Sulfamethoxazole+trimethoprim, Sulfamonomethoxine+ormetoprim,				Sulfamethoxazole+trimetoprime, Sulfadiacine+trimetoprime,	
AM-Bc	Hormones				Testosterone+estradio+ tylosin, Ractopamine+tylsoin,			
AI				Heparin+levomenthol+salicylate,				
AS	DI					Glutaraldehyde+benzalkonide,		
DI			o-dichlorbenzene+quinomethionate,					
Vitamins			Vitamin A+D3+E+B2+B6+B12,					
Vitamins	Minerals		Vitamins+(Fe, Cu, Co, Mn, Zn),					
Gastrointestinal			Berberine+ursodeoxycholic acid+ Geranium herb+Scopolia extract,					
Hormones			Progesterone+estradiol, Serum-/chorionic-gonadotrophin,		Estradiol+testosterone,			
Cardiology				Benazepril+spironolactone,				

Table 3.1 Guidance/guidelines already in place

Item	Title (attach PDF file or URL)	Product category	Brief summary (within 100 words)
#1	Guidance on pharmaceutical fixed combination products (EMEA/CVMP/83804/05) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004645.pdf	X	In the EU, fixed combination products must be justified, i.e. offer an advantage over their active substances, when used as single substance products. The guideline outlines the EU data requirements for efficacy, safety and residues documentation for veterinary medicinal products, containing 2 or more active substances. It also explains the criteria to justify a fixed combination.
#2	Questions and answers on the CVMP guideline on fixed combination products (EMEA/CVMP/83804/2005) http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/10/WC500116977.pdf	AP	A separate Q&A document is available addressing in more detail the justifications for a fixed combination product, and the specific rationale for antiparasitic combinations. The document is currently under revision.
#3	European Legislation (EU Directive 2001/82/EC), (p16)Art 13b http://ec.europa.eu/health/files/eudralex/vol-5/consol_2004/dir_2001_02-dir_2004_28-cons_en.pdf	X	"In the case of VMPs containing active substances used in the composition of authorised VMP but not hitherto used in combination for therapeutic purposes, the results of safety and residue tests, if necessary, and new pre-clinical tests or new clinical trials relating to that combination shall be provided …, but it shall not be necessary to provide scientific references relating to each individual active substance."
#4	CVM GFI #24 Drug Combinations for Use in Animals http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052666.htm	X	This guideline is the Bureau of Veterinary Medicine's interpretation of this regulation. Specifically, prior to approval of a drug combination, the sponsor is to submit information and data to demonstrate that the combination of drugs provides a benefit that cannot be obtained by the use of each of the drugs individually (i.e., each drug has made a contribution).

Table 3.2 Guidance/guidelines already in place

Item	Title (attach PDF file or URL)	Product category	Brief summary (within 100 words)
#5	World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline: Anthelmintic combination products targeting nematode infections of ruminants and horses (Vet Parasitol Vol190 (2012) 306-316) http://www.sciencedirect.com/science/article/pii/S0304401712004591#	AP	This guideline is intended to provide a scientific basis to recommend globally applicable principles governing the approval of anthelmintic combination products with two or more constituents with similar spectra of activity from different pharmacological classes in fixed-dose, single dosage formulations for use in ruminants and horses. The application dossier for combination product should include: 1) Justification for the combination, 2) Dose determination data, 3) Target animal safety and pharmacokinetic data, 4) Product bioequivalence, 5) Dose confirmation studies, and 6) Field efficacy studies; in addition to the existing requirements already established for single-constituent active products.
#6	Australian Pesticide and Veterinary Medicine Agency: Preamble for WAAVP guideline: Combination anthelmintic products for ruminants and horses http://apvma.gov.au/node/894.#Geometric_versus_arithmetic_means	AP	This notice is stating the Australian government has adopted the WAAVP combination products guideline (2012) and provides the following additional guidance to assist applicants conducting trials for the registration of such products in Australia. • WAAVP second edition guidelines for evaluating the efficacy of anthelmintics in ruminants (bovine, ovine, caprine) • WAAVP second edition guidelines for evaluating the efficacy of equine anthelmintics • VICH GL7 : Efficacy of anthelmintics general requirements • VICH GL12 : Efficacy of anthelmintics for bovines • VICH GL13 : Efficacy of anthelmintics for ovines • VICH GL14 : Efficacy of anthelmintics for caprines • VICH GL15 : Efficacy of anthelmintics for equines

Table 4 Structural comparison of guidance/guideline already in place

Parts	#1: EMEA/CVMP/83804/05	#4: FDA/ CVM GFI #24	#5: WAAVP/Australia
Introductory part	♦ Introduction (background) ♦ Scope ♦ Legal Basis	♦ Introductory statement	♦ Introduction (general) ♦ Combining anthelmintics: current situation ♦ Objectives of the anthelmintic combination guideline
Discussion part	♦ Justification of the Combination ➢ Interactions ➢ Indications ➢ Potential Advantages • Improvement of activity • Broadening of the activity spectrum • Use of a combination product versus combined use of single substances ♦ Risk-Benefit assessment	➢ Non-Interference ➢ Rational ➢ Titration ➢ Ranges ➢ General Efficacy ➢ Combination Claims and Treatment Comparisons	♦ Rationales for the use of anthelmintic combination products ➢ Managing existing resistance ➢ Delaying anthelmintic resistance ➢ Specific targeting of dose-limiting species ➢ Maximizing breadth of spectrum ➢ ♦ Concerns about fixed-dose anthelmintic combination products ➢ Drug–drug interactions ➢ Common mechanisms of resistance ➢ Best-practice management of combination anthelmintics
Dossiers Requirements part	♦ General requirements ➢ New fixed combination products ➢ Combination products that meet the criteria for well established use ➢ Combination products that meet the criteria for generic application ♦ Specific Requirements ➢ Specific requirements for safety and residues documentation ➢ Specific requirements for preclinical and clinical documentation (Preclinical data, Dose-finding, Tolerance, Clinical data, Resistance, Exceptions)		➢ Justification for the combination ➢ Dose determination data on the anthelmintic constituent actives in the combination ➢ Target animal safety and pharmacokinetic data showing non-interference and acceptable safety ➢ Product bioequivalence ➢ Dose confirmation studies ➢ Field efficacy studies
Others	♦ Combination packs		♦ Conclusions