



Concept Paper for a general guideline on pharmaceutical combination products

VICH Task Force for the development of a general combination guideline

1. Introduction

At the 3rd VICH Outreach Forum (VOF) meeting which was held in conjunction with the 29th Steering Committee (SC) meeting in Auckland, New Zealand on November 11-14, 2013; China PR submitted a draft concept paper (CP) entitled “Need to Develop a VICH Guidance for Efficacy Studies for Combination Drug Products”¹. The SC applauded the first concrete proposal for a VICH topic from a VOF member.

The SC recognized that the CP addresses an important topic of relevance to VICH, although the proposed scope was considered to be too broad. The SC therefore agreed to create a TF chaired by JMAFF with the mandate to develop a discussion paper proposing a more focused scope for the development of a VICH Guideline (GL) for combination products².

The TF first surveyed which classes of products consisting of “fixed combination of two or more APIs in one sales unit of single registration/approval” are available in different regions/countries to prioritize the target products for the (one or several) GL(s). From the survey results, antiparasitic (AP) products represented the most common fixed combination veterinary medicines, closely followed by antimicrobial (AM) combinations. Nevertheless, some members denied support for the development of a specific GL for AM combination products, as these regulators did not wish to encourage new developments that could conflict with principles of prudent use of AMs.

The TF also explored the possibility of creating a general policy document. There was a broad consensus within the TF during discussion as well as SC members regarding the need for development of a general GL ahead of specific combination products GLs. Based on the discussion paper, the SC decided that the first topic to be addressed would be an internationally harmonized general combination product guideline which would draw on elements from the EU and US GLs already in place.

2. Problem statement

An important reason for developing VICH GL for studies for pharmaceutical combination products is that there is currently no globally applicable guidance, but numerous combination products are authorized throughout the world (approximately 80 combinations for APs only) and the number is growing year by year.

Firstly, it is essential to consider the potential justifications for combining active ingredients, which should be based on valid therapeutic principles. This should be the main focus of the guideline. In addition, in view of this and other challenges involved in the development of combination products, and the complexity of efficacy and pharmacokinetic evaluation required for combination products, there is a need to better define and describe the technical efficacy study requirements for the regulatory approval of these products.

In particular, several questions may need to be answered in providing a more complete framework of data requirements; including:

- How efficacy should be comprehensively assessed, taking into consideration the presence of different active ingredients and potentially multiple mechanisms of action, as well as more than one therapeutic effect.
- How to best investigate drug-to-drug interactions including synergy, potentiation, additive and interference effects; and their impact not only on the efficacy, but also on safety aspects (particularly, residue depletion) of combination products, and
- How to address the risk of development of resistance to the ingredients.

3. Impact for public health, animal health and animal welfare

Sharing a VICH-agreed scientific basis for the assessment of combinations of different classes of ingredients will give assurance that veterinary fixed combination medicines will be developed and evaluated appropriately.

An agreed VICH GL for combination products will limit duplication of studies in different regions and therefore further the 3Rs agenda for reducing animal use in studies .

4. Anticipated benefit to:

-Industry and Other Interested Parties;

The VICH GL will provide a harmonized framework for addressing the benefits and risks of combination products

-Regulatory Authorities;

The GL will provide a harmonized framework for assessment by regulators, reducing the time for reviewing technical dossiers and reaching conclusion on the benefit/risk of products.

5. Discussion

The TF found that there are two general combination product GLs, one published by EU/CVMP (#1) and the other by USFDA/CVM (#2). Table 1 shows a structural comparison of the two guidelines; the main body of #1 is comprised of “Discussion” and “Dossier requirements” parts, providing overall guidance on this kind of application, while #2 has a “Discussion” but not a “Dossier requirements” part. The discussion part of each document consists of similar elements; these include the interaction or interference of the APIs, rationale or advantage for the combination, how to assess the product efficacy and safety.

The major difference between them seems that #1 considers not only efficacy but also safety aspects, while #2 is focused on efficacy only. The discussion part in #2 gives an extremely precise description of efficacy evaluation for various combination patterns of active ingredients in the “Combination Claims and Treatment Comparison” section.

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

The TF felt that it would be practical to create an internationally harmonized new VICH GL by extracting elements from both GLs (#1 and #2). In line with this approach, although safety fell outside the initial scope of the draft guideline proposed by China PR, the TF considers that the components for “safety” and furthermore “risk of resistance” in #1 are important additional topics for consideration and should be briefly addressed in the guideline. In addition, the principle of the 3Rs (animal welfare) should be taken into consideration when developing the guideline.

Table 1, Structural comparison of guidance/guideline already in place

| GLs Parts | #1: Guidance on pharmaceutical fixed combination products (EMA/CVMP/83804/05) ³ | #2: Drug Combinations for Use in Animals (FDA/CVM GFI #24) ⁴ |
|--------------|--|--|
| Introductory | <ul style="list-style-type: none"> ◆ Introduction (background) ◆ Scope ◆ Legal Basis | <ul style="list-style-type: none"> ◆ Introductory statement |
| Discussion | <ul style="list-style-type: none"> ◆ Justification of the Combination <ul style="list-style-type: none"> ➢ Interactions ➢ Indications ➢ Potential Advantages <ul style="list-style-type: none"> • Improvement of activity • Broadening of the activity spectrum • Use of a combination product versus combined use of single substances (e.g., reduction of total number of injection sites) ◆ Risk-Benefit assessment | <ul style="list-style-type: none"> ➢ Non-Interference ➢ Rational ➢ Titration ➢ Ranges ➢ General Efficacy ➢ <u>Combination Claims and Treatment Comparisons</u> |

| | | |
|-------------------|--|--|
| Test Requirements | <ul style="list-style-type: none"> ◆ General requirements <ul style="list-style-type: none"> ➤ 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 <ul style="list-style-type: none"> ➤ Specific requirements for <u>safety</u> and <u>residues</u> documentation ➤ Specific requirements for preclinical and clinical documentation (Preclinical data, Dose-finding, Tolerance, Clinical data, Resistance, Exceptions) | |
| Others | ◆ Combination packs | |

6. Recommendation (action plan, issues to be addressed, mandate, etc.)

I. General pharmaceutical combination products VICH GL

The SC has already decided the first topic to be addressed is an internationally harmonized general combination product guideline. It was recognized that the EU and US GLs are currently the only general GLs on combination products that the TF members were aware of and it would be practical for the putative EWG to create an internationally harmonized new GL by extracting elements from both GLs. The “Dossier Requirements” part in EU guidance should be converted into “Test Requirement” in accordance with the principle of VICH which is focusing on the technical requirement but not the dossier structure.

The main focus should be the justification for the fixed combination as already discussed in sections 2 and 5. Other topics relating to safety should be only briefly addressed, as existing VICH guidance would remain applicable (GL43 on target animal safety, GL48 for residue studies and GLs 6 and 38 for environmental risk).

II. Specific combination VICH GL

A specific combination GL is out of the scope of the current concept paper. However, during the creation of the Discussion Paper, the TF felt that antiparasitic products should be prioritized when creating a class-specific combination guideline and the guideline should take into account the control of drug resistance as a central proposition. The SC suggests that the topic of antiparasitic combination should be addressed by the Anthelmintics EWG in the future, focusing on the issues that are not covered by the putative general combination VICH GL.

The GL will not address issues of particular relevance to antimicrobial combinations as VICH does not wish to encourage the development of antimicrobial combinations that could be inconsistent with the principles of prudent use of antimicrobials in veterinary medicine. This does not preclude future innovations or combinations with other substances consistent with prudent use or that improve therapeutic outcome.

In time, other types of combination products may become a target for a new specific guideline based on further discussions in the VOF and the SC meetings in the future.

7. Timetable/ Milestones

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| June 2016 | Briefly review this CP at the 33rd SC / 6 th VOF meeting and initiate internal review in each country/region to include opinion of the members to the CP. |
| Feb. 2017 | The SC finalizes the CP, decide to establish an EWG for general guideline on pharmaceutical combination products and nominate the chair/topic leader. |
| Nov. 2017 | The EWG will present the first progress report to the SC. |
| June 2018 | The EWG will present the second progress report to the SC. |
| Feb. 2019 | The EWG will present step 2 document to the SC. |

8. Impact assessment for Industry and Regulatory Authority

Addressed in section 3 and 4.

9. References

- ¹ China PR, Concept paper on the Needs to Develop a VICH Guidance for Efficacy Studies for Combination Drug Products (Draft); VICH/IN/13025, October 2013.
- ² VICH Task Force for Efficacy Studies for Combination Products, Discussion Paper: Major veterinary combination products in the world and relevant guidance/guidelines in place, VICH/IN/15031, 21 Oct. 2015
- ³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004645.pdf (Accessed on 5 April, 2016)
- ⁴ <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052666.htm> (Accessed on 5 April, 2016)