Concept Paper on the Need to Develop VICH Guidance for Efficacy Studies for Combination Drug Products (Draft)

1. Introduction

Because of the development of resistance in bacteria, coccidia and helminthes, and with the goal in mind of expanding the spectrum of effectiveness for antimicrobial and antiparasitic drugs, various combination products for therapeutic and prophylaxtic uses in food animals have been authorized in a number of VICH member and observer countries. These products include combinations of antimicrobials, coccidiostats, antiparasitics, and combinations of antimicrobials and anti-inflammatories, combinations of antimicrobials with coccidiostats, etc.

There are many reasons why it is desirable to develop and use combination products. The main rationale is to produce more effective treatments. Another rationale is to simplify treatment regimens for diseased animals, especially for treating infectious diseases.

This concept paper addresses the need for VICH guidelines that cover the technical requirements for the design of clinical efficacy studies for combination drug products. Such harmonized guidelines will assist greatly in facilitating future marketing authorizations for these products.

Animal health products are typically developed by utilizing the following three different approaches:

- The individual active ingredient(s) is approved as a single ingredient products and later combined into a multiple ingredient product;
- The individual active ingredients are approved only in combination and one or more ingredients is not approved as a single ingredient;
- The individual active ingredients are approved as single ingredient products and are labeled for concurrent use but not formulated as a combination product.

2. Problem statement and discussion

The EMA's "Guideline on Fixed Combination Medicinal Products", states: "Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended when feasible."

While the EMA guidance is helpful, there is a general need for more specific and

detailed guidance. As mentioned above, the therapeutic rationale for developing combination products may be different than the rationale for developing single ingredient formulation products. For example,

- Antimicrobial combination products may be intended to expand the spectrum of effectiveness, and the results of efficacy studies may show the effects of synergy, addition, and antagonism.
- Antimicrobial/anti-inflammatory combination products may be intended to have better therapeutic effects for treating clinical mastitis or other bacterial infections.
- Antiparasitic combination products may be intended to expand the antiparasitic spectrum of effectiveness, to have synergistic effects on coccidiostats, and/or to improve feed efficiency.
- Coccidiostat/antimicrobial combination products may be intended to achieve prophylaxtic effects on the coccidiosis, to reduce the infectious disease, and/or to improve feed efficiency.

In view of these and other challenges involved in the development of combined products and the efficacy and pharmacokinetics evaluations 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 considered regarding combination products. These include:

- How the comprehensive efficacy should be assessed considering the presence of different active ingredients and potentially multiple mechanisms of action?
- How to properly assess the effects of combination products with more than two ingredients?
- How to best investigate drug-to-drug interactions including synergy, potentiation, additive and interference effects and their impact on safety and effectiveness in combination products?

Another important reason for developing VICH guidelines for efficacy studies for combination products is that there is no appropriate guidance existing at this time. This is an opportunity for the VICH countries to work together to draft such guidance.

Issues/questions to be covered in the guidelines should also notably include:

- What are the crucial points in the design of pivotal clinical studies?
- What would be an adequate clinical program to support an authorization of a particular antimicrobial combination product?

3. Recommendation

Because of the fact that there are so many possible kinds of combination products, we recommend convening an Expert Working Group to draft a guideline for the evaluation of the efficacy of only antimicrobial combination products. Other combination products could be addressed by VICH at a later date. The Expert Working Group should consist of experts in the fields of animal modeling for infectious diseases, biostatistics and with consultations of stakeholders.

4. Proposed timetable

- Consideration of this draft concept paper at the VICH Steering Committee meeting in November 2013.
- After a positive recommendation by the VICH Steering Committee, a subgroup could be created and charged with developing a more refined concept paper that would provide a more detailed scope and charge to a future Expert Working Group for consideration.
- At the 2014 VICH Steering Committee meeting a decision would be made as to whether to convene an Expert Working Group to draft a guideline.

5. Impact assessment (anticipated)

It is anticipated that these VICH guidelines will help stakeholders to adequately and most appropriately substantiate the benefit of combination products and allow for a proper benefit/risk assessment by regulators.

Appendix 1: References

Publications on the Design of Combination Drug Efficacy Trials

The design of combination drug trials is not as fully discussed in the literature as design of single drug efficacy studies. There are some recent publications that are very useful in addressing some of the challenges in combination drug efficacy clinical trials:

1. Wei, L. (2006). An efficient design for a study comparing two drugs, their combination and placebo. Statistics in Medicine 25: 2043-2058.

2. Huang, X., Biswas, S., Oki, Y., Issa, J-P. and Berry, D.A. (2007). A parallel phase I/II clinical trial design for combination therapies. Biometrics 63: 429-436

Publications on Statistical Analysis of Combination Drug Efficacy Trials

A. Evaluating of efficacy and/or superiority of a single drug combination (via the Min test)

Laska, E.M. and Meisner, M.J. (1989). Testing whether an identified treatment is best. Biometrics 45: 1139-1151.

Laska, E.M., Tang, D. and Meisner, M.J. (1992). Testing hypotheses about an identified treatment when there are multiple endpoints. Journal of the American Statistical Association, 87(419): 825-831.

Snapinn, S.M. (1987). Evaluating the efficacy of a combination drug therapy. Statistics in Medicine 6: 657-665.

B. Detecting if there is at least one superior combination among considered in the study

Hung, H.M.J. (2000). Evaluation of a combination drug with multiple doses in unbalanced factorial design clinical trials. Statistics in Medicine 19: 2079-2087.

Hung, H.M.J. (1996). Global tests for combination drug studies in factorial trials. Statistics in Medicine 15: 233-247.

Hung, H.M.J., Chi, J.Y., and Lipicky, R.J. (1993). Testing for the existence of a desirable dose combination. Biometrics 49: 85-94.

C. Identifying minimum effective and efficacious combinations

Hellmich, M. and Lehmacher, W. (2005). Closure procedures for monotone bi-factorial dose-response designs. Biometrics 6: 269-276.

Soulakova, J.N. and Sampson, A.R. (2009). On identifying minimum efficacious doses in combination drug trials. Statistics in Biopharmaceutical Research 1(1): 39-47.

Soulakova, J.N. (2009). Comparison of Several Testing Strategies for Combination Drug Efficacy Trials Based on the Closure Principle. Statistics in Medicine 28: 260-273.

D. Identifying simultaneously effective and superior combinations

Soulakova, J.N. (2009). On Identifying Effective and Superior Drug Combinations via Holm's Procedure Based on the Min Tests. Journal of Biopharmaceutical Statistics 19(2): 280-291.

Soulakova, J.N. Resampling-Based and Other Multiple Testing Strategies with Application to Combination Drug Trials with Factorial Designs. Statistical Methods in Medical Research (Accepted for 2010).

E. Identifying all superior combinations

Buchheister, B. and Lehmacher, W. (2006). Multiple testing procedures for identifying desirable dose combinations in bi-factorial designs. GMS Medical Informatics, Biometry and Epidemiology 2(2), Doc 07, 1-11. Available at http://www.egms.de/en/journals/zma/2006-2/mibe000026.shtml.

Additional Resources on Combination Drugs and Products

U.S. Food and Drug Administration:

1. Policy Fixed-Combination Prescription Drugs for Humans. Code of Federal Regulations, Title 21, Volume 5 (21 CFR 300.50). Revised April 1, 2005.

Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.

2. Guidance for Industry. Combination New Animal Drugs: Recommendations for Satisfying Approval Requirements (in draft and soon to be released).

3. Guidance for Industry #24. Drug Combinations for Use in Animals, revised October 1983.

European Guidelines:

1. Guideline on Fixed Combinations

http://www.emea.europa.eu/pdfs/human/ewp/024095en.pdf

2. ICH E 12 Principles for Clinical Evaluation of New Antihypertensive Drugs --Section 6

http://www.emea.europa.eu/pdfs/human/ich/054100en.pdf

Also read about combination products on Wikipedia.

Additional Resources on Multiple Testing Procedures

Special Issue of The Journal of Biopharmaceutical Statistics on Multiplicity Issues Multiplicity Expert web site

Chang, C-K., Rom, D.M. and Sarkar, S.K. (1996). Modified Bonferroni procedure for repeated significance testing. Technical Report 96-01, Temple University.

Chen, J.J. and Wang, S-J. (2002). Testing for treatment effects on subsets of endpoints. Biometrical Journal 44(5): 541-557.

Cohen, A., Gatsonis, C. and Marden, J. (1983). Hypothesis tests and optimality in discrete multivariate analysis. Studies in Econometrics, Time Series and Multivariate Statistics. New York: Academic Press.

Dudoit, S., Shaffer, J.P. and Boldrick, J.C. (2003). Multiple Hypothesis Testing in Microarray Experiments. Statistical Science, 18(1): 71-103.

Ge, Y., Dudoit, S. and Speed, T.P. (2003). Resampling-based multiple testing for microarray data analysis. Test, 12(1): 1-77.

Hochberg, Y. (1988). A sharper Bonferroni procedure for multiple tests of

significance. Biometrika 75: 800-802.

Hochberg, Y. and Rom, D.M. (1995). Extensions of multiple testing procedures based on Simes test. Journal of Statistical Planning and Inference 48: 141-152.

Hochberg, Y. and Tamhane, A.C. (1987) Multiple Comparison Procedures. Wiley: New York.

Holm, S. (1979). A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics 6: 65-70.

Horn, M., Vollandt, R. and Dunnett, C.W. (2000). Sample size determination for testing whether an identified treatment is best. Biometrics 56: 879-881.

Huang, Y. and Hsu, J.C. (2007). Hochberg's step-up method: cutting corners off Holms step-down method. Biometrika, 94(4): 965-75.

Lehman, E.L. (1952). Testing multiparameter hypotheses. The Annals of Mathematical Statistics, 23(4): 541-552.

Samuel-Cahn, E. (1996). Is this Simes improved Bonferroni procedure conservative? Biometrika, 83: 928-933.

Schumi, J. and DeGruttola, V. (2008). Resampling-based analyses of the effects of combinations of HIV genetic mutations on drug susceptibility. Statistics in Medicine, Available at www.interscience.wiley.com , DOI: 10.1002/sim.3181

Simes, R.J. (1986). An improved Bonferroni procedure for multiple tests of significance. Biometrika 73: 751-754.

Snapinn, S.M. (1987). Evaluating the efficacy of a combination drug therapy. Statistics in Medicine 6: 657-665.

Westfall, P.H. and Young, S.S. (1993). Resampling-Based Multiple Testing: Examples and Methods for p-Value Adjustment. John Wiley & Sons, Inc.

Appendix 2: Possible considerations for efficacy requirements

- **Antimicrobials combination**
  - Basis of combination
    - ✓ In vitro inhibition test: by disk diffusion test/broth dilution test, to demonstrate synergy, additive, antagonism effect.
    - ✓ Resistance prevention: Selection Index (MPC/MIC).
    - ✓ PK/PD profile: Concentration dependent type and time dependent type. For the concentration dependent type antimicrobials combination products, what parameter may be crucial? For the time dependent type antimicrobials combination products, what parameter may be crucial?

- Efficacy evaluation
  - ✓ Criteria of cure: how to define eradication, recover, recurrent
  - ✓ Infected case study-*inclusion/exclusion criteria*, evaluation criteria
  - ✓ Natural clinical case study-*inclusion/exclusion criteria, evaluation criteria*

- **Coccidiostats combination**

- Basis of combination
  - ✓ How to define prevention, treatment and prophylaxis effects
  - ✓ How to define synergists that may help to improve the coccidiostatics effects.
- Efficacy evaluation
  - ✓ Criteria of cure: how to define eradication, recover, recurrent.
  - ✓ Infected case study- *inclusion/exclusion criteria.*
  - ✓ Natural clinical case study- *inclusion/exclusion criteria.* evaluation criteria: applicability of Merck index?

- **Antiparasitics combination**

- Efficacy evaluation
  - ✓ Criteria of cure: how to define eradication, recover, recurrent
  - ✓ Infected case study- *inclusion/exclusion criteria*
  - ✓ Natural clinical case study- *inclusion/exclusion criteria*

- **Antimicrobials combined with anti-inflammatories**

  - ✓ Criteria of cure: how to define eradication, recover, recurrent, how to artificially duplicate the diseases model.
- Efficacy evaluation
  - ✓ Criteria of cure: how to define eradication, recover, recurrent
  - ✓ Infected case study- inclusion/exclusion criteria
  - ✓ Natural clinical case study- inclusion/exclusion criteria

- **Coccidiostats combined with antimicrobials**

  - ✓ Criteria of cure: how to define eradication, recover, recurrent, how

to artificially duplicate the diseases model.

- Efficacy evaluation
  - ✓ Criteria of cure: how to define eradication, recover, recurrent
  - ✓ Infected case study- inclusion/exclusion criteria
  - ✓ Natural clinical case study- inclusion/exclusion criteria