International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH/20/004

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Final

CONCEPT PAPER

for a Guideline for Safety Evaluation of Biotechnology-derived/Biological products

(Items that complement the existing VICH-GL on target animal safety test)

1. Introduction

Since the 30th Steering committee (SC) meeting in Brussels in June 2014, the SC has been discussing the development of VICH Biotechnology-derived/Biological products guideline (Bio-products GL).

For the background survey, the SC firstly assessed the needs for guidelines on Veterinary Bio-products among the members. At the 31st SC meeting in Washington DC, JMAFF presented the report which was showing approximately half of VICH members were using ICH Bio-products GLs, nevertheless the members felt difficulty in applying ICH Bio-products GLs to VMPs, especially on GL S6 (R1) “Preclinical safety evaluation of biotechnology derived pharmaceuticals” due to the different situation between Human Medicinal Products (HMPs) and Veterinary Medicinal Products (VMPs). In addition, the survey indicated that majority of the members supported a development of relevant VICH GLs. Taking these, JMAFF therefore recommended at the 33rd SC the development of a new GL for the safety evaluation of Veterinary Bio-products.

2. Problem statement

There are no harmonized regulatory standards for safety testing in veterinary Bio-products . While case by case approach should be utilized to determine safety studies of Bio-products, developing of guiding principles and common understanding among the regions would be beneficial for both regulatory authority and industry to avoid confusion and unnecessary repetition of controversial disputes. It should be noted direct conversion from ICH GL to VICH GL would not be appropriate, but an adaption to the VMP sector must be carefully considered when developing a new GL.

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

A veterinary Bio-products GL is expected to facilitate a development of new VMPs in this field. Harmonization of standards can reduce the number of animals used in the study by avoiding unnecessary animal studies.

4. Anticipated benefit

For target animal safety evaluation of veterinary Bio-products, a study design has been determined by case-by-case basis until now, but it is a time-consuming process. Harmonization of test requirement standards leads to simplification of determining acceptable study design and to shorter development and registration period (from submission to approval).

5. Discussion

(1) Concept for preclinical safety GL for Bio-tech VMPs

The different situation of preclinical and clinical studies in HMPs and VMPs are shown in Fig.1.

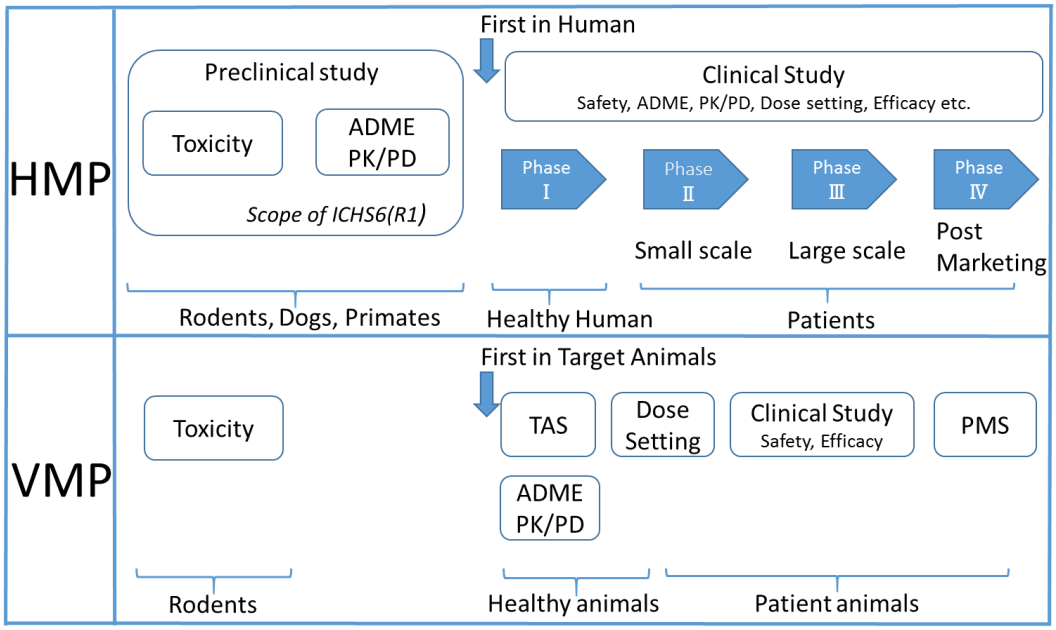

Fig.1 Preclinical and Clinical studies in HMPs and VMPs

For HMPs, “Preclinical safety study” is performed to obtain crucial safety information before “First in Human” (Phase I clinical study). They include whole set of toxicity tests, absorption/ distribution/metabolism/excretion (ADME), pharmacokinetics/pharmacodynamics (PK/PD). In the field of VMPs, many of these studies could be performed by using target animals rather than rodents. In consequence, the use of laboratory animals (mainly rodents) would usually be limited to some toxicity studies for VMPs, only for those cannot be evaluated by target animal tests. Therefore, a limited number of items appeared in ICH 6S (R1), e.g., immunogenicity, immunotoxicity, reproductive performance and developmental toxicity test would be selected, while most of the other items can be covered by target animal tests, e.g., target animal safety tests (TAS), pharmacology test and ADME, will not be included.

As shown in Table 1 just for example, 9 out of 14 items appeared in ICH S6(R1) may be covered by regular target animal tests. Further, selection of items included in the veterinary Bio-products GL should precisely be investigated by a putative EWG.Table.1 An *example of selection* of items to be included in VICH GL from ICH S6(R1)

No.	*Items appeared in ICH S6(R1)*	*Need for VICH-GL*	*Remarks*
1	Biological Activity / Pharmacodynamics	No	Covered by TA[*1]-Pharmacology, TA-ADME
2	Animal Species /Model Selection	No	Covered by TAS
3	Number /Gender of Animals	No	Covered by TAS
4	Administration /Dose Selection[*2]	No	Covered by TAS , TA-Pharmacology
5	Immunogenicity	Yes	Serum samples from TAS test can be used (no separate animal test would be needed)
6	Safety Pharmacology	No	Covered by TA-Pharmacology,
7	Exposure Assessment[*3]	No	Covered by TA-Pharmacology, TA-ADME
8	Single Dose Toxicity Studies	Yes	May provide useful data to evaluate "*Dose to Toxicity"* relationship.
9	Repeated Dose Toxicity Studies	No	Covered by TAS
10	Immunotoxicity Studies	Yes	If a product is intended to stimulate or suppress the immune system.
11	Reproductive Performance and Developmental Toxicity Studies[*4]	Yes	If a product may affect in fertility, fetus and neonate.
12	Genotoxicity studies	No	When a product is not expected to interact directly with DNA or chromosomal materials.
13	Carcinogenicity Studies	Yes	For growth factors and immunosuppressors which may support or induce proliferation of transformed cell and neoplasia
14	Local Tolerance Studies	No	Covered by TAS

*1: TA= target animal
*2: Dose Selection and Application of PK/PD Principles, Duration of Studies, Recovery, Exploratory Clinical Trials
*3: Pharmacokinetics and Toxicokinetics, Assays, Metabolism
*4: Fertility, Embryo-Fetal Development and Pre/Post-Natal Development, Timing of Studies

(2) Scope of the putative GL

The scope of ICH S6 (R1) cannot be directly applicable as discussed above; still it might be useful to review these at this moment for information purpose. Examples of products within or outside the Scope are shown inTable.2. The scope of biotechnological / biological VMP (GL17 and GL40) should be referenced (Table 2 and 3).

Table 2, Scope of ICH S6(R1) “Preclinical safety evaluation of Biotechnology-Derived pharmaceuticals”

Within the scope	Cytokines / Plasminogen activators / Recombinant plasma factors / Growth factors / Fusion proteins / Enzymes / Receptors / Hormones / Monoclonal antibodies / Recombinant DNA protein vaccines / Chemically synthesised peptides / Plasma derived products / Endogenous proteins extracted from human tissue / Oligonucleotide drugs
Outside the scope	Antibiotics / Allergenic extracts / Heparin / Vitamins / Cellular blood components / Conventional bacterial or viral vaccines / DNA vaccines / Cellular and gene therapies

Table 3, Scope of VICH GL17 “Stability Testing of New Biotechnological / Biological Veterinary Medicinal Products”

Within the scope	cytokines / growth hormones / growth factors / insulins / monoclonal antibodies / vaccines which consist of well-characterized proteins or polypeptides
Outside the scope	antibiotics / heparins / vitamins / cell metabolites / DNA products / allergenic extracts / conventional vaccines / cells / whole blood / cellular blood components

Table 4, Scope of VICH GL40 “Test Procedures and Acceptance Criteria for New Biotechnological / Biological Veterinary Medicinal Products”

Within the scope	cytokines / growth hormones / growth factors / insulins / monoclonal antibodies
Outside the scope	antibiotics / heparins / vitamins / cell metabolites / DNA products / allergenic extracts / vaccines / cells / whole blood / cellular blood components

Most VICH member countries/regions have relatively little experience in the evaluation of Bio-products and consequently they are still in the process of developing their thinking in this area. In order to allow progress at the VICH level it is therefore proposed that the scope of VICH guidance to be developed in the first instance should be limited and manageable. An appropriate scope for an initial guideline is considered to be the target animal safety (not the human food safety) of monoclonal antibodies.

Successful development of a guideline with limited scope could then provide a basis from which to move forward with development of guidelines focused on other types of products; e.g., cytokines, growth hormones, growth factors and insulins.

The scope could be gradually expanded to the novel therapeutics including cell-based products in the future. Human safety evaluation could also be considered at a later stage.

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

According to the EU comment received on Feb 18, 2018, it will be appropriate to take longer timeline so that each member should have more of an opportunity to develop their own thinking in relation to safety evaluation for relevant product types.

In the “VICH Priorities 2016-2020”, the following is clearly stated: “Analyse the need for developing guidance on registration requirements for veterinary novel therapy products and initiate the development, or adaptation, of guidance for those types of products considered of greatest strategic importance to VICH”. In this context, development of Bio-products GLs should continuously be considered.

Development of a guideline is now recommended, focusing on the target animal safety evaluation of veterinary medicinal products containing monoclonal antibodies.

7. Timetable/ Milestones

June 2018	Each country/region will circulate the current version of the CP in the authority / member companies.
Feb. 2019	Each country/region will report a feedback, if any, from their members at the SC meeting,
2020	Each country/region will report the feedback from their members to the SC. The SC will then finalize the CP, and either mandate the Safety EWG or establish a new EWG to create a new VICH guideline.
2021	The EWG will present the first progress report to the SC.
2022	The EWG will present step 2 document to the SC.