VICH/97/061
May 2005
Revision 1 - FINAL

# NOTES ON THE FORMAT AND STYLE OF VICH GUIDELINES

The following guidance, which has been agreed to by the VICH Steering Committee is intended to be followed by VICH Expert Working Groups (EWGs), and especially the topic-leader when drawing up or revising VICH drafts. The objective is to adopt a uniform structure for future VICH Guidelines.

The format which is proposed is based on a similar guidance document from ICH, itself based on a review of the main elements in the existing ICH guidelines. It is recommended that, as far as possible all guidelines consist of the following sections:

**TITLE PAGE**
**1. Introduction**
1.1. Objective(s) of the guideline
1.2. Background
1.3. Scope of the guideline
1.4. General Principles if appropriate
**2. Guidelines**
**3. Glossary**

## NOTES ON THE FORMAT

### TITLE PAGE

Each successive draft of the guideline should have a separate title page which clearly identifies the document by giving:

- the full title of the draft guidelines or text
- a draft number identifying the version of the text
- the date of circulation of the draft

A “model” title page is annexed to this paper (Annex 1).

As the guideline is developed, the title page should also include a list of contents giving the headings and sub-headings used in the draft.

### 1. INTRODUCTION

#### 1.1. Objective(s) of the guidelines

Brief introductory comments giving the purpose for which the guideline has been drawn up (for new topics, this should be based on the “Problem statement/Objectives” in the concept paper).

#### 1.2. Background

This section should include information which helps to put the guideline into context, including, for example, whether it is to be read in conjunction with any other guideline (rule or regulation).

### 1.3. Scope of the guidelines

This should be included in order to define the precise application of the guideline. In view of the differences in legislation and competent authorities covering various categories of products in different regions (e.g. biologicals, feed additives), it is essential that, on all general guidelines, the scope be precisely described. The scope should state the range of tests and/or products to which the guideline applies, and whether there are any exclusions. For example, the scope of the first Stability Guideline was limited to tests on new chemical entities and their formulations; existing formulations and variations were excluded.

### 1.4. General Principles

This section should be included if there are general considerations which apply to the whole technical area which is addressed by the guideline. For example, the Impurities guideline includes a section on the "Classification of Impurities" which would be appropriate to a "General Principles" section.

## 2. GUIDELINES

This is the "operative" section of the text, giving specific recommendations and guidance on technical matters, for example the way in which tests should be carried out and/or the way data should be presented. The format and structure of the guideline (headings, subheadings, etc.) will vary according to the nature of the subject, but there should be a clear separation between:

- *specific guidance and recommendations*
- *commentaries on the guidance*

Notes and examples, which do not form part of the specific guidelines, should be clearly differentiated from the "operative" text. The extensive use of footnotes or end notes is not, however, recommended. It is preferable to include the supplementary information within the guideline but differentiate it by the use of a combination of formatting and headings ("*Note:", "Example:",* etc.)

## 3. GLOSSARY

Consideration should always be given to the need for a glossary defining the way in which certain terms are used for the purpose of the guideline. Where possible, the glossary should be defined at the outset and it is important to cross refer to glossaries in all other VICH guidelines in order to avoid conflicting definitions.

## SIGN OFF SHEET

A sign-off sheet with the signatures of all experts (Step 2 or Step 5) should be annexed to the title page. A "model" sign-off sheet is annexed (Annex 2).

## POINTS TO AVOID

### References

References to published papers and the scientific literature are not usually appropriate for a document which is destined to end up as a regulatory guideline. If useful, references to existing, recognised, international guidelines may be included.

### Summary and conclusions

It is not necessary to summarise the effect and implications of the guideline in the VICH text, as this is not appropriate for a document which is destined to become a regulatory guideline.

### Description of the VICH process

Reference should not be made in the texts themselves to discussions in the EWG or the "Steps" in the VICH process. The texts are ultimately destined for publication as official regulatory guidelines, etc. where such information would not be appropriate.

## STYLE

- Guidelines should be in clear plain English free from jargon.
- Guidelines should normally be written in the "third person", predominantly in the passive tense. The imperative tense is not appropriate (e.g. "Retain all samples for 5 years"). The first person must never be used e.g. "In our opinion …" "We agreed …".
- The final texts will become regulatory guidelines. Clarity is more important than literary style. The repetitive use of a phrase or word is acceptable in order to convey the correct meaning and changes should not be made merely for the sake of variety.

The following gives guidance on the use of the terms "must", "should" and "may" in the English language drafts. Please note that translation of these terms into Japanese is particularly difficult as many similar terms exist. It is therefore important that the meaning is unambiguous in the original text.

**must** : has a mandatory meaning. Therefore, it would not normally be used in a "guideline" where, by definition, there should be flexibility.

**should** : (e.g. 'Data should be provided on …") is used where it is a strong recommendation, but not an absolute requirement. It leaves open the possibility that the requirement could be waived if there is adequate justification. The verb "ought" has a similar meaning but is rarely correct in a formal document (i.e. "Data ought to be provided on …" is not appropriate).

**may** : (e.g. "Data may be provided on …") is used where there is a clear option regarding the provision of information. Such statements would often be qualified by an "if" clause ("Data may be needed to demonstrate … if …"). The verb "might" has a similar meaning, but implies a slightly weaker option (i.e. "Data might be needed on …").

# EXAMPLES FROM EXISTING GUIDELINES

## 1. INTRODUCTION

### 1.1 Objective(s) of the Guideline

Example taken from VICH GL37 (Safety): *Studies to evaluate the Safety of Residues of Veterinary Drugs in human Food: Repeat-Dose Chronic Toxicity Testing*

*A variety of toxicological evaluations are performed to establish the safety of veterinary drug residues in human food. The objective of this guideline is to establish recommendations for internationally harmonized repeat-dose (chronic) toxicity testing.*

### 1.2 Background

Example taken from VICH GL33 (Safety: General Approach): *Studies to evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing*

The hazards associated with the consumption of food containing residues of veterinary drugs are generally assessed in laboratory animals treated with the drugs. International harmonization of testing requirements aims to assure that the development and registration of valuable animal drugs is achieved with maximum efficiency. The efficiency of the approval process has an impact on the expenditure of resources, time from discovery to new product approval, and the introduction of innovative drugs into the market.

*The current toxicological testing requirements for veterinary drugs are based on the toxicological tests for human medicines, food additives and pesticides. This guideline indicates those tests particularly relevant to the identification of a no-observed adverse effect level (NOAEL) for veterinary drugs.*

*The appropriateness of a test for the purpose of assessing human food safety is determined by its ability to predict an adverse effect in humans. The selection of concise and appropriate tests was of major concern and a regimen was selected based on a minimum number of tests after consideration of extensive historical data and a review of widely accepted protocols. To increase the chance of identifying a potential adverse effect, both rodent and non-rodent models are included in the testing approach. Additional studies, such as tests for effects on human intestinal flora, may be used to evaluate compound specific endpoints. A testing approach is designed to determine a dose that causes an adverse effect and a dose that can be identified as the NOAEL. A NOAEL is used to establish a human acceptable daily intake (ADI), which represents the amount of drug that can be safely consumed by a person on a daily basis for a lifetime.*

### 1.3 Scope of the Guideline

Example taken from VICH GL3 (Stability 1): *Stability Testing of New Veterinary Drug Substances and Medicinal Products*

*The guideline primarily addresses the information required in Registration Applications for new molecular entities and associated drug products. The requirements for biotechnological/ biological products and medicated premix products will be the subject of separate guidelines.*

*This guideline does not currently seek to cover the information required for abbreviated or abridged applications, variations, clinical trial applications, etc.*

*The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three areas of the EC, Japan and the USA. The mean kinetic temperature in any region of the world can be derived from climatic data (Grimm, W. Drugs Made in Germany, 28, 196-202, 1985 and 29, 39-47, 1986).*

### 1.4 General Principles

Example taken from VICH GL10 (Impurities New Substances): *Impurities in New Veterinary Drug Substances*

*Impurities may be classified into the following categories:*

- *Organic Impurities (Process and Drug Related)*
- *Inorganic Impurities*
- *Residual Solvents*

*Organic impurities may arise during the manufacturing process and/or storage of the new drug substance. They may be identified or unidentified, volatile or non-volatile, and include:*

- *Starting Materials*
- *By-Products*
- *Intermediates*
- *Degradation Products*
- *Reagents, Ligands and Catalysts*

*Inorganic impurities may derive from the manufacturing process. They are normally known and identified and include:*

- *Reagents, Ligands and Catalysts*
- *Heavy Metals*
- *Inorganic Salts*
- *Other Materials (e.g., Filter Aids, Charcoal, etc.)*

*Solvents are organic or inorganic liquids used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished.*

## 2. GUIDELINES

Example taken from VICH GL28 (Safety: Carcinogenicity): *Studies to evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing* which where edited to include the Note with the text.

***Existing relevant guidelines***

*The OECD Test Guideline 451 "Carcinogenicity Studies"[1] contains study protocol guidelines and approaches for testing chemicals for carcinogenicity using experimental animals. This document serves as the basis for carcinogenicity testing of veterinary drugs with clarifications outlined in the following paragraphs.*

*Note: Information derived from a combined assay for carcinogenicity and chronic toxicity (OECD Test Guideline 453 "Combined Chronic Toxicity/Carcinogenicity Studies"[2] ) would also be acceptable.*

## 3. GLOSSARY

Example taken from VICH GL17 (Stability 4): *Stability Testing of New Biotchnological/Biological Veterinary Medicinal Products*

***Conjugated Product***

*A conjugated product is made up of an active ingredient (e.g., peptide, carbohydrate) bound covalently or noncovalently to a carrier (e.g., protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.*

***Degradation Product***

*A molecule resulting from a change in the drug substance (bulk material) brought about over time. For the purpose of stability testing of the products described in this guideline, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis). For biotechnological/biological products, some degradation products may be active.*

***Impurity***

*Any component of the drug substance (bulk material) or drug product (finished product) that is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.*

**ANNEX I**

**VICH GL1 (VALIDATION 1)**
**October 1997**
**For consultation at Step 4 - Draft 1**

# VALIDATION OF ANALYTICAL PROCEDURES : DEFINITION AND TERMINOLOGY

Recommended for Consultation
at Step 4 of the VICH Process
on 21 August 1997
by the VICH Steering Committee

**ANNEX 2**

# DRAFT SIGN OFF BY THE WORKING GROUP
# STEP … DOCUMENT

**Topic**

**Reference** _____

**Subject** _____

Draft No. _____ Dated _____

**EUROPE**

| | |
|---|---|
| **EU** _____<br>*(NAME)* | **IFAH-Europe** _____<br>*(NAME)* |

**JAPAN**

| | |
|---|---|
| **JMAFF** _____<br>*(NAME)* | **JVPA** _____<br>*(NAME)* |

**USA**

| | |
|---|---|
| **US FDA** _____<br>*(NAME)* | **AHI** _____<br>*(NAME)* |

**OTHER EXPERT (if applicable)**

| | |
|---|---|
| _____<br>*(NAME)* | _____<br>*(NAME)* |

**Date :**