VICH/IN/08020
Dated 01/12/08

Concept Paper that Proposes to Revise GL 33, General Approach to Animal Testing, to Include References to the 3 R's Principle

Introduction

Animal welfare is an important concern of both regulators and industry in the VICH regions and observer countries. In respect to safety testing of chemical substances efforts have been and are continuing to be made on national and international levels to refine, reduce and replace animal testing (3 R's) by developing alternative approaches.

At the 18th VICH Steering Committee, the SC members discussed an EU Discussion Paper that suggested a need to initiate a review of all relevant existing VICH guidelines to be assured that they conform to the most recent developments in alternative testing. While there was no conclusion about whether the scope of this review, the SC members agreed to continue further discussions before the next SC meeting.

At the 19th SC meeting, the members discussed what would be the most appropriate action for VICH to undertake. The FDA proposed that a general policy statement supporting the 3Rs principles be drafted for consideration, which could be adopted by written procedure. The FDA presented information about FDA's participation in the U.S. Interagency Coordination Committee on the Validation of Alternative Methods (ICCVAM) which included the international harmonisation activities of ICCVAM, ECVAM and JaCVAM. After this discussion, the SC members supported having the SC draft a statement indicating that VICH supports the 3Rs rule and encourages the development of international harmonisation in this area. It was also concluded that the SC should give a mandate to each newly formed EWG to consider the 3R's rule in the development of new VICH GLs. It was agreed that the VICH would issue a general statement of principle regarding adherence to the 3R's principle, would enable access to the information available on the appropriate websites in the 3 regions, and would take measures to ensure that there are ways to check that regional agencies fulfill their legal obligations to use validated alternative testing.

The following VICH Statement of Principle has been included on the VICH public website:

"Statement of Principle for VICH – Alternatives to Animal Testing

> At its 19th meeting on 23-24 January 2007 in Washington D.C., USA, the VICH Steering Committee reiterated its ambition to minimise animal testing and specifically expressed its support for the 3Rs principle – replacement, refinement and reduction of animals in research.
>
> VICH has always striven to eliminate repetitious and unnecessary testing through harmonisation of regulatory requirements for the registration of veterinary products, a goal that undoubtedly leads to a reduction in the number of animals used for product development and registration.

VICH/IN/08020
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While the validation of alternative testing protocols[1] falls outside the remit of VICH, the Steering Committee recognises that the international status and influence of VICH provide a unique opportunity to encourage the use of validated alternative methods. To this end, Expert Working Groups (EWGs) developing guidelines involving animal experimentation have a specific responsibility to consider animal welfare, and particularly the possibilities for replacement, refinement and reduction of animal testing."

[1] Validation of alternative testing protocols is the responsibility of regional bodies; ECVAM in Europe, ICCVAM in the USA and JaCVAM in Japan.

Problem statement, including references to existing technical and legislative requirements in the different regions

At the 21st SC meeting, FDA suggested reconvening the EWG in order to analyse in general the latest scientific evolution regarding safety issues and adding the referencing to the minimisation of animal testing (VICH 3R's policy) to the VICH safety GLs. The SC agreed to include a reference to the VICH 3R's policy in VICH GL 33, *Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human food: General Approach to Testing.* The SC furthermore stated that the wording adopted for the VICH public on the 3R's policy statement should be used as the basis for the amendment. The SC encouraged FDA to provide a Concept Paper as soon as possible. The SC agreed that the review should be a minor change procedure that could be done by written agreement.

Impact for public health, animal health and animal welfare

Public health and animal health will be assured when any alternative tests have been appropriately validated. Animal welfare will be assured by adherence to the 3R's rule.

Anticipated benefit to:

- **Industry and Other Interested Parties**
- **Regulatory Authorities**

Animal welfare is an important concern of both regulators and industry in the VICH regions and observer countries. In respect to safety testing of chemical substances, efforts have been and are continuing to be made on national and international levels to refine, reduce and replace animal testing (3 R's) by developing acceptable alternative approaches. To express this policy as an affirmative statement in GL 33, the General Approach to Safety Testing Guideline, will help to assure adherence to this policy. This will benefit both the industry and regulators.

- **Discussion**

The VICH SC concluded that GL 33, the General Approach to Safety Testing Guideline, should include information that makes reference to the VICH 3 R's policy. Proposed language for revising GL 33 is contained below under the Recommendation Section.

VICH/IN/08020
Dated 01/12/08

Concept Paper that Proposes to Revise GL 33, General Approach to Animal Testing, to Include References to the 3 R's Principle

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

It is recommended that the "Introduction" section of GL 33 be revised as follows:

1. INTRODUCTION

1.1. Objective of the guideline

This guideline outlines a testing approach to assure the safety of human food derived from animals treated with veterinary drugs. The tests should provide an adequate amount of toxicological data to ensure human food safety, while reducing the number of animals used in testing and conserving resources. Whenever possible, flexibility, minimum number of animals, as well as alternative in vivo and in vitro tests have been recommended.

VICH seeks to minimise animal testing and supports the 3R's principle – replacement (replace with non-animal system or with phylogenectically lower species), refinement (lessen or eliminate pain or distress in animals) and reduction (lower the number of test animals needed) of animals in research. One of the expressed goals of VICH is to strive to eliminate repetitious and unnecessary testing through harmonisation of regulatory requirements for the registration of veterinary products, a goal that undoubtedly leads to a reduction in the number of animals used for product development and registration. Whenever possible, flexibility, minimum number of animals, as well as alternatives to in vivo and in vitro tests, have been recommended.

When carrying out the studies recommended below due regard for the welfare of the study animals should be given. The use of animals in the studies described below should adhere to these protocols and should conform to general ethical standards and to the national standards for the use and care of experimental animals.

While the validation of alternative testing protocols falls outside its remit, VICH recognises that the international status and influence of VICH provide a unique opportunity to encourage the use of validated alternative methods[1]. To this end, the Safety EWG that developed these guidelines involving animal experimentation has exercised its responsibility to consider animal welfare, and particularly the possibilities for replacement, refinement and reduction of animal testing.

VICH/IN/08020
Dated 01/12/08

Concept Paper that Proposes to Revise GL 33, General Approach to Animal Testing, to Include References to the 3 R's Principle

VICH exercises it continuing obligation to monitor the development of alternative testing protocols that have been validated and to amend its guidelines where appropriate to assure that they conform to the most recent alternative testing developments.

[1] Validation of alternative testing protocols is the responsibility of regional bodies; ECVAM in Europe, ICCVAM in the USA and JaCVAM in Japan.

- **Timetable**

It is proposed that these revisions could be accomplished by written procedure and would not require the convening of a physical EWG. If the SC agrees with the proposal contained in this Concept Paper, each VICH party should identify the appropriate individual(s) that would represent the membership of a reconstituted Safety EWG in order to consider this Concept Paper and the proposed amendment to GL 33 that is contained herein. It is recommended that the work of the Safety EWG could be accomplished in approximately 3 months and could be undertaken entirely through written procedure.

- **Milestones**

None necessary.

- **Impact assessment for Industry**

None necessary

- **Impact assessment for Regulatory Authorities**

None necessary

- **References to literature, existing relevant international guidelines or standards (e.g. ICH, OECD, CODEX, JECFA,…).**

For relevant international and national references, please see below the VICH *Discussion Paper on the Development on Guidance Regarding Alternatives to and Reduction of Animal Testing* and its Annex. This paper was used previously by the VICH SC for developing the VICH 3 R's Policy Statement.

VICH/IN/08020
Dated 01/12/08

Concept Paper that Proposes to Revise GL 33, General Approach to Animal Testing, to Include References to the 3 R's Principle

Discussion Paper on the Development on Guidance Regarding Alternatives to and Reduction of Animal Testing

Introduction

Animal welfare is the subject of societal concerns in the VICH regions and observer countries and has found entry in various legislations and regulations in these. In respect to safety testing of chemical substances efforts have been and are continuingly being made on national and international level to refine, reduce and replace animal testing (3 Rs) by developing alternative approaches.

In developing VICH guidelines for the establishment of harmonised data requirements for the registration of veterinary medicinal products the aspect of reducing animal testing was considered specifically in some cases, e.g. for the testing strategy for developmental toxicity testing (GL 32), or where internationally agreed test protocols, such as OECD guidelines, referenced in the VICH guidelines take specific account of approaches to reduce animal testing. However, no systematic approach has yet been undertaken at VICH to review the availability of approaches that allow for further refinement, reduction and replacement of animal testing regarding all parts of a dossier, where this would be possible, and to prepare guidance on the use and acceptability of certain alternative tests and/or approaches.

It is recognised that alternative testing methods may be available for some parts of a dossier. However, companies will in general not use alternative testing methods because there is no harmonised guidance ensuring their acceptance. In order to for Industry to be motivated/be able to use alternative tests and/or approaches for their dossier requirements some type of assurance is needed that their proposed alternative test or approach will be accepted for regulatory purposes. At the 17th VICH Steering Committee meeting it was agreed that the EU would prepare a discussion document aimed for the VICH to set up guidance for alternative testing methods or appropriate testing strategies aimed to reduce animal testing; the end objective being the reduction of animal testing. Contributions have been received from Canada, JMAFF, JVPA and IFAH Europe (attached).

Proposal

It is proposed that VICH would formally embark on the topic of alternative approaches of animals testing, within its Strategy for the years 2006-2010. The aim would not be to develop new guidelines but rather to identify existing validated alternative tests and appropriate testing strategies/study designs aimed to reduce animal testing and to provide guidance on the use and acceptance of these testing methods in marketing authorisation dossiers.

The following components are proposed as main part of the activity:

VICH/IN/08020
Dated 01/12/08

Concept Paper that Proposes to Revise GL 33, General Approach to Animal Testing, to Include References to the 3 R's Principle

1. Establishing a compilation of existing validated[2] alternative approaches to animal testing.

2. Giving the mandate to all EWGs developing new guidelines involving animal testing to consider specifically the aspect of animal welfare and possibilities for refinement, reduction and replacement of animal testing.
3. Reviewing existing VICH guidelines, as to whether they require update or revision to take account of available alternative approaches to animal testing or refinement and reduction of animal testing.

4. Establishing a mechanism by which the compilation of validated alternative approaches to animal testing is kept up-to-date.

While these activities relate to the work of several EWGs it would be probably necessary that a specific EWG be established to co-ordinate the task. This EWG could in particular be in charge of the establishment of a list of validated alternative methods. Possibly such a group could operate without face-to-face meetings.

This EWG would need to consist of experts in relation to both testing for pharmaceuticals and biologicals. The role of the EWG experts may be more of a co-ordinating role rather than being the expert on the specific testing protocols – classical or alternative - under consideration. However, they would probably need to liaise with specialised experts in these fields.

Re.1: In order to establish a compilation of validated alternative approaches to animal testing as a starting point the VICH partners should compile and submit lists of the validated test approaches used in their country with references.

Re 2: Once a compilation of validated alternative approaches to animal testing has been established, the listed methods would need to be related to existing VICH guidelines, or new topics or topics under consideration.

The actual work on the revision of an existing guideline should be undertaken following the same procedure as any other revision or update of a guideline.

Re 3: The reviewing of existing VICH guidelines, as to whether they require update or revision to take account of available alternative approaches to animal testing or refinement and reduction of animal testing, could be undertaken when monitoring existing guidelines.

The aim to refine, reduce and replace animal testing needs to balance the substantial technical and scientific challenges with the necessary requirements of consumer, user, target animal and environmental safety.

[2] In the EU alternative testing methods are primarily validated through the European Centre for Validation of Alternative Methods (ECVAM) and the European Pharmacopoeia.

Annex

Report on Guidelines and Policies Implemented in Canada Regarding Alternatives to Animal Tests

Veterinary Drugs Directorate
January 24, 2006

Regulatory Animal Testing in Canada

Approximately 250,000 animals are used annually for regulatory testing in Canada, according to the Canadian Council on Animal Care. The federal agencies which request that animal studies be done in order to evaluate the safety and efficacy of veterinary drugs and biologics are the Veterinary Drugs Directorate and the Veterinary Biologic Section, respectively.

The Veterinary Drugs Directorate (VDD) is part of the Health Products and Food Branch of Health Canada. The VDD ensures the safety of foods such as meat, milk, eggs, fish and honey from animals treated with veterinary drugs. The VDD also ensures that veterinary drugs sold in Canada are safe and effective for animals.

The Veterinary Biologic Section (VBS) of the Animal Health and Production Division, within the Canadian Food Inspection Agency, is responsible licensing and regulating the safety of veterinary biological products in Canada.

Regulatory Requirements

1) Veterinary Drugs Directorate:

A new veterinary drug application submitted to the VDD must satisfy all the requirements under the *Food and Drugs Act and Regulations* which are administered by Health Canada. The VDD document Draft Guidance for Industry: Preparation of Veterinary New Drug Submissions (http://www.hc-sc.gc.ca/dhp-mps/consultation/vet/consultations/past-anterieures/vet/nds-pdn_indust_prep_e.html) outlines the data required to assess target animal safety, human safety (if applicable) and efficacy of the new drug.

In regards to safety studies, this document makes the following recommendations:
"Due regard should be given to the welfare of the study animals. The use of animals for research and testing should conform to the rigorous ethical standards that are compatible with the goals of science for benefitting humans or animals. Those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information. For standards for use and care of animals a reference may be made to the Canadian Council on Animal Care's Guide to the Care and Use of Experimental Animals."

2) Veterinary Biologic Section

According to the *Canadian Health of Animals Act and Regulations*, veterinary biologics must be demonstrated by the manufacturer to be pure, potent, safe and effective when used in the target species according to the label recommendations. A licensing submission to the VBS must also contain supporting data demonstrating that the product can be manufactured and used without adversely affecting animal health, human health, food safety or the environment.

The documents, VBS Guideline 3.17: Guide for Reporting Laboratory and Field Efficacy Trials (http://www.inspection.gc.ca/english/anima/vetbio/info/vb317e.shtml) and VBS Guideline 4.8: Safety Requirements for Veterinary Biological Products in Canada

(http://www.inspection.gc.ca/english/anima/vetbio/ref/vb408e.shtml) include the following statement:
"All aspects involved in the proposed use of animals in the efficacy trials/safety tests and trials, must meet the standards and regulations for the care and maintenance of experimental animals as described by the Canadian Council on Animal Care, relevant provincial legislation and local animal care authorities."

Canadian Council on Animal Care

The Canadian Council on Animal Care (CCAC) is the national peer review agency responsible for setting and maintaining standards for the care and use of animals in research, teaching and testing throughout Canada. The purpose of the CCAC is to ensure that the use of animals employs optimal physical and psychological care according to acceptable scientific standards, and to promote an increased level of knowledge, awareness and sensitivity to relevant ethical principles.

CCAC guidelines and policies are developed in response to current and emerging needs of the research community, advances in laboratory animal care and in conjuction with the needs of the CCAC Assessment Program. The programs of the CCAC apply to all animals used for the purposes of testing and manufacturing veterinary drugs and biological products. The guidelines and policies of the CCAC are the only documents developed and implemented in Canada that provide guidance on the use of alternatives to animals testing, i.e. replacement, refinement, and/or reduction alternatives to tests using animals.

Guidance and Policy Documents Implemented in Canada which reference Alternatives

CCAC *Guide to the Care and Use of Experimental Animals: Vol. 1, 2nd Edn., 1993*
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GUIDES/ENGLISH/toc_v1.htm

CCAC *Guide to the Care and Use of Experimental Animals: Vol. 2, 1984*
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GUIDES/ENGLISH/TOC_V2.HTM

CCAC guidelines:

*Animal use protocol review, 1997**
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/PROTOCOL/PROTOGDE.HTM

*Choosing an appropriate endpoint in experiments using animals for research, teaching,and testing, 1998***
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/ENDPTS/APPOPEN.HTM

CCAC policy statements:

Ethics of Animal Investigation, 1989
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICIES/ETHICS.HTM

Social and Behavioral Requirements of Experimental Animals, 1990
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICIES/SABREA.HTM

Terms of Reference for Animal Care Committees, 2000
http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICIES/TERMS00E.HTM

The appendix may be consulted for a listing of key points from the above documents.

* Will be considered as a potential international reference document at the next meeting of the International Council for Laboratory Animal Science (ICLAS) Working Group on Harmonization of Guidelines.
** Recognized by ICLAS as an international reference document.

Appendix: Key points from Guidance and Policy Documents

CCAC *Guide to the Care and Use of Experimental Animals: Vol. 1, 2nd Edn., 1993*
• references CCAC position statements including the Ethics of Animal Investigation, and the Social and Behavioral Requirements of Experimental Animals
• establishes standards for laboratory and farm animal facilities, e.g. cage dimensions, and environmental considerations, e.g. noise levels
• addresses social and behavioral requirements of animals including environmental and behavioral enrichment
• provides recommendations for surgery, pain control, anesthesia and euthanasia

CCAC *Guide to the Care and Use of Experimental Animals: Vol. 2, 1984*
• provides guidelines for the care and use of representative classes of animals
• requires commitment to the Russell-Burch tenet of “Replacement, Reduction and Refinement”

CCAC guidelines on: *Animal use protocol review, 1997*
• animals should be used only if the researcher’s best efforts to find an alternative have failed
• each protocol must be reviewed annually and must take into consideration changes in standards and guidelines, and developments in the replacement, reduction and refinement of experimental animal use
• a continuing sharing of knowledge, review of the literature and adherence to the Russell-Burch “3R” tenet of “Replacement, Reduction and Refinement” are requisites

• those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information
• all members of Animal Care Committees (ACC) and all investigators have the responsibility to continuously refine procedures
• provides guidance on replacement alternatives, animal model selection, reduction of animal use, refinement of experimental technique, setting endpoints, physical restraint, invasive/stressful procedures, euthanasia

CCAC guidelines on: *Choosing an appropriate endpoint in experiments using animals for research, teaching, and testing, 1998*
• in experiments involving animals, any actual or potential pain, distress or discomfort, should be minimized or alleviated by choosing the earliest endpoint that is compatible with the scientific objectives of the research
• the requirement for death as an endpoint in any experiment is questioned
• recommends the use of pilot studies, using a small number of animals to help determine morbidity, time course of effects and frequency of observations required to set earlier endpoints
• provides guidelines for selecting appropriate endpoints in specific areas of biomedical research and testing, e.g. acute and chronic toxicity testing
• lists species specific signs of pain and/or distress
• supplies examples of observational checklists used to determine endpoints

CCAC policy statement on: *Ethics of Animal Investigation, 1989*
• animals should be used only if the researcher's best effort to find an alternative have failed
• a continuing sharing of knowledge, review of the literature and adherence to the Russell-Burch "3R" tenet of "Replacement, Reduction and Refinement" are requisites
• those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information
• animals should be maintained in a manner that provides for their physical comfort and psychological well-being
• animals must not be subjected to unnecessary pain or distress
• pain and distress must be minimized both in intensity and duration
• alternative endpoints in studies that previously have required continuation until the death of an animal should be sought
• animals experiencing severe, unrelievable pain or discomfort should immediately be humanely killed
• physical restraint should only be used after alternative procedures have been fully considered and found inadequate

CCAC policy statement on: *Social and Behavioral Requirements of Experimental Animals, 1990*
• a social environment is desired for each animal which will allow basic social contacts and positive social relationships
• caging should be enriched appropriately for the species
• chronic isolation as a method of accommodation, should not normally occur

CCAC policy statement on: *Terms of Reference for Animal Care Committees, 2000*
• one of the ACC's responsibilities is to require all animal users to complete an animal use protocol form which includes a description of possible replacement, refinement,

and/or reduction alternatives and justification if they are not used, or a description of an applicant's efforts to find alternatives

• experimental protocols should indicate that the planned animal use does not exceed the regulatory requirements and should provide a description of the endpoints

• it is the responsibility of the ACC to establish procedures to ensure that unnecessary pain or distress in avoided, anesthesia and analgesia are properly and effectively used, and all due consideration is given to animal welfare including environmental enrichment

• the ACC must review and assess all animal use protocols, with particular emphasis on the CCAC's *Guide to the Care and Use of Experimental Animals*, the *Ethics of Animal Investigation* policy statement and the *Guidelines on: Animal use protocol review* as well as on all other CCAC guidelines and policy statements

• the ACC should ensure that all animal users have the opportunity to become familiar with the CCAC's *Guide* and *Ethics* statement and all other CCAC guidelines and policy statements, and should sponsor seminars and workshops on the use of animals in science and the ethics of animal experimentation

• the ACC must also ensure that policies are established and implemented including the requirement that all animal care and animal experimentation are conducted according to CCAC guidelines and policies

Current status of animal testing alternatives in the developmental stage and quality testing for veterinary medicinal products in Japan

1. Animal tests required for application for approval of drugs

Test data listed below are required when making an application for approval of new veterinary medicinal products in compliance with the Pharmaceutical Affairs Law.

a. Background of origin or discovery (development) of drug
b. Physical, chemical, or biological properties, including specifications and test methods
c. Production method
d. Stability
e. Toxicity
f. Safety in target animals
g. Pharmacological action
h. Absorption, distribution, metabolism and excretion
i. Clinical trials
j. Residue study

Among the tests to be conducted in the developmental stage, e, f, g, h, i and j require to use animals. As the data on b and d of biological products, animal tests may be required to establish the quality test method and to evaluate the quality of the drug products.

2. Laws concerning animal testing alternatives

Law for Humane Treatment and Management of Animals (Law No.105, enforced in 1973) which is under the jurisdiction of the Ministry of the Environment stipulates prevention of cruelty to animals, appropriate handling of animals, and other matters concerning zoophily.

This law was amended in June 2005. The amended law specifies that consideration should be given to the so-called 3R principle (Refinement: relief of distress; Replacement: use of alternative methods; and Reduction: reduction of the number used) when animals are used for scientific purposes. Although relief of distress (Refinement) was prescribed before amendment, the amended law including the 3R principle will be enforced in June 2006.

It will be necessary to develop veterinary medicinal products and deal with approved drug products in consideration of the Replacement and Reduction.

12

3. Current status of activities toward introduction of alternative methods in the developmental stage and quality testing stage of veterinary medicinal products

1) Pharmaceutical products such as general medicaments and antibiotic agents

The data on the tests using animals such as toxicity testing for drug products for human use can be used if the veterinary medicinal product has something in common with drug products for human use.

It is extremely rare to develop an alternative method unique to veterinary medicinal products.

2) Biological products such as vaccine preparations

For the reasons of protection of animals, improvement of the efficiency of test methods, testing cost reduction, or assurance of safety of test practitioners, efforts have been made for development or improvement to achieve a test that requires no target animals or a method that involves no animals.

When a test animal other than the target animal is sensitive to the vaccine strain or a strain for challenge study, a method of quality testing using the test animal is developed (e.g. mice are used in potency test using inactivated blackleg vaccine).

For some inactivated vaccines, challenge study or antibody measurement test using test animals has been switched to antigen quantitative test (e.g. antigen quantitative test of inactivated rabies vaccine).

In Vitro Test or Alternative Test Guidelines Authorized in Japan

1. **Mutagenicity test –Bacterial reverse mutation test (Ames test)**
2. **Mutagenicity test-Chromosomal aberration test on cultured Chinese Hamster cells**
3. **Mutagenicity test-Mouse lymphoma assay**
4. **Phototoxicity test using Balb / c 3T3 cells**
5. **Endotoxin detection test-Testing by Limulus Amoebocyte Lysate (JP)**
6. **Cytotoxicity test on medical plastic containers (JP)**
7. **Local lympho node assay (LLNA)**
8. **Skin corrosive test using TER or skin model**

Reference ; Current Major Topics for Validation in Japan

1. **Dermal corrosivity test method using a new skin model**
2. **Dermal irritation test method using skin model**
3. **Photo-toxicity test using battery of yeast and RBC**
4. **Non-RI LLNA (ATP contents or BrdU uptake)**
5. **h-CLAT (in vitro sensitization assay)**
6. **In vitro or in vivo comet assay**

A stably transfected ER alpha mediated reporter gene assay

Veterinary Sector Legislation and Testing Requirements vis-à-vis Animal Use

Potential New Medicines for Veterinary Use within the EU and Worldwide	
Sector Legislation	
Legislation	Directive 2001/82/EC as amended by Directive 2004/28/EC CVMP Guidelines, European Commission guidelines, including 'Notice to Applicants'; European Pharmacopoeia monographs FDA /CVM Guidelines
EU DG Responsible	Enterprise and Industry, with input from DG SanCo on consumer safety
Testing Obligation (explicit or implicit)	Explicit in most cases.
Prescribed Animal Tests	Yes, except for investigatory studies which are designed to address specific issues
Secondary Guidance	VICH but becomes primary guidance once adopted Codex/JECFA (Joint expert committee on food additives)
GLP	Yes (and vet. GCP)
Explicit Reduction Goal	No, but Recital 25 states "avoid repeating tests on animals." In some countries (e.g. UK) it is a requirement to consider 3Rs when conducting studies
Reference to 86/609/EEC	Yes (in Annex 1 to Directive 2001/82/EC as amended)
Test Ban (EU/Member States)	No
Mandated Alternatives (obligatory or facultative)	Several EP veterinary vaccine monographs now detail alternative test methods. In most cases these are facultative, although, a few are obligatory.
Human Testing (permitted)	May be necessary for 'user safety' studies
Other Observations	
Key Tests/Key Characteristics of the Sector (emphasis on those using most animals)	Routine use of rodent species. Tissue residue depletion studies in food-animals (pig, sheep cow, poultry). In the target species, healthy animals are used for a range of required studies e.g. safety studies at multiples of dose, pharmacokinetic studies, induced disease studies to determine dose and confirm efficacy. Batch release tests e.g. for vaccines. N.B. In addition to the above, veterinary clinical trials (equivalent to Phase III) naturally require testing on the diseased target species (or in the case of vaccines in healthy animals to prevent naturally occurring disease),, but should not necessarily be seen in the same light as "animal experimentation" as they should benefit
Trends or Developments Potentially Increasing Animal Use (especially when initiated by Regulators or Competent Authorities)	Release of new and updated guidelines can result in 'regulatory creep' and the need for additional animal testing'; VICH process must avoid harmonisation to the highest common denominator. Increasing caution regarding toxicology and target animal safety resulting in increased animal testing. Lack of willingness to accept clinical trial data as primary evidence of efficacy unless supported by extensive data using induced disease (which may not anyway be representative of natural disease).
Opportunities for Improvements	- Animal numbers and humane endpoints. CVMP Statistical guideline requiring 'non-inferiority' comparisons largely transcribed into vet sector from human sector; pushes up number of animals needed per group, yet this type of information is not necessary for vet sector (no national patient reimbursement schemes) - Opportunities: o Identification of areas of overlap, duplication and inconsistency in

	regional guidelines (via VICH) o Critical review of the scientific basis for existing, new or draft GLs o Development strategies and timing of studies o Pharmaceutical sector acceptance of validated alternative or refined tests used for chemicals e.g. local lymph node assay, - Reduction in retesting by authorities via Official Control Authority Batch Release for certain vaccines (article 82 of the Directive). - In the vaccine sector, the possibility of moving from final batch potency testing to a consistency of production approach.
Examples of Best Practice or Good Regulation (especially with potential for reapplication to other sectors)	FDA and EMEA guidance on abbreviated packages to support products with limited markets (minor uses and minor species = MUMS), although the application of these guidelines is currently very restricted (especially in relation to minor-use indications) and their wider application would both reduce experimental animal use and increase availability of medicines.